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Exploring evidence for neurorehabilitation advancements

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Exploring evidence for neurorehabilitation advancements

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Editorial: Exploring evidence for neurorehabilitation advancements

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Editorial on the Research Topic
Exploring evidence for neurorehabilitation advancements

1 Introduction

Neurorehabilitation is an important field dedicated to the restoration of function following nervous system injuries such as stroke or spinal cord injury. However, evidence regarding its efficacy and optimal approaches remains in the developmental stage, and many challenges persist. This Research Topic, titled "*Exploring evidence for neurorehabilitation advancements*," compiles the latest research findings in the field of neurorehabilitation and provides a comprehensive examination of a wide range of themes including physical therapy, occupational therapy, neuromodulation technology, virtual reality, nutrition, and assessment methodologies. In this Editorial, we provide an overview of the key contributions of the 25 papers included in this Research Topic and discuss the latest advances in neurorehabilitation, their academic and clinical significance, and future challenges and prospects. By synthesizing the findings from each study, we aimed to clarify the current state of the neurorehabilitation field and offer guidance for future research and clinical applications.

2 Overview

This Research Topic includes a diverse array of contributions, from systematic reviews and meta-analyses to clinical trials, study protocols, and theoretical proposals, each focusing on a different aspect of neurorehabilitation.

First, this Research Topic contains several systematic reviews and meta-analyses evaluating the effects of rehabilitation interventions. One notable example is a meta-analysis that quantitatively examined the effects of physiotherapy on degenerative cerebellar ataxia (Matsugi et al.), which demonstrated significant improvements in gait ability and coordinated movement with physiotherapy interventions, supporting the utility of rehabilitation interventions for progressive diseases. In addition, a review by Lou et al. assessing the safety and efficacy of initiating very early rehabilitation in patients with acute stroke reported that early intervention may improve functional outcomes. Furthermore,

Jiang et al. performed a comprehensive analysis of the effects of body-weight-supported treadmill training on balance and walking function in patients with stroke and found that rehabilitation interventions using assistive devices, such as body weight support systems, can contribute to improvements in balance and walking speed. However, a systematic review by Sánchez-González et al., which critically reevaluated the evidence for Vojta therapy, pointed out a lack of high-quality evidence regarding the clinical efficacy of the Vojta method for developmental and neurological disorders, highlighting the need for more rigorous validation. Additionally, a systematic review and meta-analysis of the effects of fully immersive virtual reality training in patients with mild cognitive impairment (MCI) showed that VR-based interventions led to significant improvements in the cognitive function of patients with MCI, supporting the effectiveness of rehabilitation approaches that leverage digital technology (Yu et al.).

This Research Topic also focused on non-invasive and invasive neuromodulation techniques. Regarding vagus nerve stimulation (VNS), an extensive literature review Korupolu et al. summarized strategies combining VNS with rehabilitation and reported its potential effects on motor recovery after stroke. In addition, a bibliometric study by Li et al., which analyzed research trends in transcranial magnetic stimulation (TMS) over the past 30 years, showed that the application of repetitive TMS (rTMS) for disorders such as aphasia and dysphagia has recently become a hot topic; however, further evidence is required for clinical implementation. Similarly, in another bibliometric analysis, Liu et al. examined global research trends in theta burst stimulation (TBS) and reported the recent increase in publications and major researcher networks. These reviews provide insights into the research trends for novel technologies and inform the planning of future research strategies.

This Research Topic also included a study that analyzes research trends in neurorehabilitation using bibliometric methods. Zhang and Zhu analyzed the literature trends in exercise therapy research for neurological diseases from 2000 to 2024 and reported a remarkable increase in the number of related publications and an expansion of collaborative relationships among major countries. Similarly, Hu et al. identified research hotspots in the field of microRNA studies for spinal cord injury, demonstrating that this field is gaining international attention for research on the molecular mechanisms of neural regeneration. Through these bibliometric analyses, the current global expansion of the evidence base in the field of neurorehabilitation and the directions of emerging research questions have been clarified.

Several original research studies have evaluated the effectiveness of novel rehabilitation approaches. For example, a randomized controlled trial by Sassmann et al. investigating electrical stimulation therapy for chemotherapy-induced peripheral neuropathy demonstrated a significant reduction in sensory impairment and pain, suggesting the potential of rehabilitation interventions to improve the quality of life of cancer survivors. Furthermore, in a primate model, Yan et al. implemented a novel approach aimed at upper limb functional recovery by applying epineural stimulation to the distal brachial plexus and showed that placing an electrode through a single axillary incision allowed selective activation of a broad range of muscles from the fingers to the upper arm. This finding suggests new possibilities for the application of invasive neuromodulation in the rehabilitation of severe paralysis. In another study, Sawai et al. compared the effects of different attentional foci (internal vs. external focus) on postural control in young and older adults and found that the predominant attentional focus significantly influenced standing balance in older adults, highlighting the importance of attentional focus in rehabilitation in this population. In a study by Valladares et al. investigating rehabilitation outcomes and related factors in stroke survivors, upper limb dexterity and motor impairment were assessed longitudinally, showing that improvements in fine motor skills either preceded or were strongly correlated with overall motor recovery. Furthermore, a prospective study by Rasová et al. observed that in patients with subacute stroke, intensive and comprehensive rehabilitation led to significant improvements in upper extremity muscle strength, dexterity, and independence in activities of daily living, with these effects particularly pronounced when intervention was initiated within a few weeks post-stroke.

Rehabilitation for COVID-19 sequelae has been addressed as a new challenge. Jöbges et al. evaluated the effects of inpatient rehabilitation in patients with post-COVID conditions (long COVID) (the PoCoRe study) and reported improvements in cognitive function and psychiatric symptoms, suggesting that comprehensive rehabilitation may be effective in alleviating long-term COVID symptoms. Demonstrating the role of rehabilitation in managing persistent symptoms of such emerging infectious diseases is important for meeting post-pandemic healthcare needs.

A review of the assessment methods for rehabilitation is also included. Wu and Jin conducted a systematic review of various scales for evaluating post-stroke fatigue in accordance with the COSMIN guidelines, comparing the reliability and validity of current measures and summarizing their strengths and weaknesses for clinical use. Similarly, a scoping review by Chen et al. on the impact of nutritional status on rehabilitation outcomes in patients with stroke indicated that patients with malnutrition tended to experience delayed functional recovery, underscoring the importance of nutritional management along with rehabilitation interventions. Furthermore, Guo et al. developed a novel nomogram to predict functional outcomes at 6 months post-intervention in patients with aneurysmal subarachnoid hemorrhage and reported high predictive accuracy. This prognostic tool is expected to provide clinicians with valuable information for early risk assessment and the planning of more effective rehabilitation strategies.

This Research Topic also included multiple protocol papers for future clinical trials, introducing efforts aimed at generating new evidence. For example, the study protocol by Wang et al., which outlines a large-scale trial using transcutaneous auricular vagus nerve stimulation (taVNS) in patients with disorders of consciousness, planned a multicenter double-blind randomized controlled trial with 382 participants and raised expectations for evaluating a novel treatment for severe disorders of consciousness. Additionally, Lee et al. presented a multicenter RCT protocol introducing personalized repetitive transcranial magnetic stimulation (rTMS) to enhance upper limb function in patients with stroke, an innovative attempt to verify whether an optimized stimulation protocol tailored to each patient can

augment rehabilitation outcomes. Furthermore, a crossover trial protocol proposed by Xu et al. examined the effects of deep brain stimulation (DBS) in the mesencephalic locomotor region on gait function in patients with post-stroke hemiplegia, exploring the potential of a new therapy that combines surgical intervention with rehabilitation. Other protocols include a study by Xiao et al. that aimed to improve post-stroke upper limb paresis using a closed-loop taVNS device and a protocol by Reeder et al. that evaluated the implementation process of a comprehensive program integrating discharge planning and rehabilitation (the HOME Rehab program). These forward-looking studies on advanced rehabilitation techniques and their feasibility indicate that the field of neurorehabilitation is still in the process of building an evidence base and that deeper knowledge is being pursued through high-quality clinical research.

Finally, an intriguing study offered a novel theoretical proposal. Nakano et al. focused on the developmental mechanisms of interhemispheric interactions in the motor cortex of healthy individuals and proposed a theoretical model in which a new bimanual coordination training program leveraged these mechanisms to improve the paretic hand function. This study provides an innovative perspective by harnessing cerebral plasticity and developmental principles in stroke rehabilitation that may influence future research directions.

In summary, the 25 papers gathered on this Research Topic provide a broad spectrum of insights into neurorehabilitation, from basic science to applied clinical practice. Although each study addresses different target areas or intervention methods, they collectively contribute to the common goal of advancing evidence-based neurorehabilitation practices.

3 Recent advances in neurorehabilitation and their significance

Among the recent advances highlighted in relation to this Research Topic, improvements in both the quality and quantity of evidence are foremost. The growing collection of systematic reviews and meta-analyses integrated evidence of intervention effects not apparent in individual studies, thereby establishing a foundation for clinicians to select treatments based on scientific evidence (Jiang et al.; Matsugi et al.). For instance, providing quantitative evidence for the effectiveness of rehabilitation for cerebellar ataxia and the efficacy of body-weight–supported treadmill training offers clear support in areas that previously tended to rely on experience. In addition, progress has been made in elucidating the factors that influence rehabilitation outcomes, such as post-stroke fatigue and nutritional status (Wu and Jin; Chen et al.), thereby leading to renewed recognition of the importance of holistic approaches.

On the technological front, the application of neurotechnology in rehabilitation has become a prominent trend in recent years. Clinical studies on non-invasive brain stimulation (e.g., TMS/TBS) and vagus nerve stimulation (VNS) are increasing annually (Li et al.; Liu et al.), and multiple related papers have been published on this Research Topic. In particular, with regard to VNS, both a synthesis of existing studies (Korupolu et al.) and new efforts in device development and stimulation optimization (Xiao et al.) indicate that the use of neuromodulation technologies in rehabilitation is accelerating. Such cutting-edge technologies open new possibilities for addressing challenges such as severe paralysis and disorders of consciousness that were previously difficult to treat (Wang et al.; Xu et al.), and they serve to expand the horizons of neurorehabilitation.

Furthermore, the personalization and precision of rehabilitation medicine represents an important advancement. As seen in the protocol by Lee et al., the concept of individualized interventions, such as adjusting brain stimulation parameters for each patient, is emerging. This approach seeks to tailor rehabilitation strategies to each patient's specific brain network state rather than using one-size-fits-all interventions. It can potentially achieve greater efficacy and reduce side effects, thereby leading to more efficient training regimens.

Clinically, the effectiveness of comprehensive and intensive approaches has been reaffirmed (Rasová et al.; Jöbges et al.). Intensive rehabilitation by a multidisciplinary team and integrated programs during inpatient stays promote the recovery of upper limb function and activities of daily living and are beneficial even for patients with complex sequelae affecting cognitive, physical, and mental functions. These findings highlight the importance of rehabilitation delivery systems and support the appropriateness of early intensive interventions (Lou et al.).

Finally, bibliometric studies have underscored the global expansion of neurorehabilitation research and the importance of international collaborations (Hu et al.; Li et al.; Liu et al.; Zhang and Zhu). Analyses of highly productive countries and research networks provide a foundation for invigorating future international collaborations and information sharing. Moreover, tracking the evolution of hot topics can inform strategic planning to allocate research resources to address emerging questions (e.g., application of rTMS for aphasia or dysphagia).

As described above, the recent advances presented in papers on this Research Topic hold multifaceted significance. They include the enhancement of the scientific evidence base, introduction of cutting-edge technologies, personalization of treatments, value of comprehensive interventions, and promotion of research from an international perspective. Neurorehabilitation was once a field heavily reliant on experiential knowledge. However, a key message gleaned from this Research Topic is that it is steadily transitioning toward evidence-based practices.

4 Challenges and future research directions

The findings highlight remaining challenges. First, as noted in several review articles, high-quality evidence is lacking in several areas. For example, even if an intervention is reported to be effective, it is often supported by a limited number of RCTs or studies in small samples. A review addressing Vojta therapy demonstrated the fragility of its evidence base (Sánchez-González et al.), and further large-scale trials are required for the application of VNS in rehabilitation as well (Korupolu et al.). Therefore, it

is necessary to reinforce these weak evidence areas through large multicenter trials and meta-analyses.

Second, in terms of technological development, the challenge lies in conducting clinical studies to verify the safety and efficacy of the new devices and stimulation methods. Promising concepts, such as closed-loop taVNS devices, have been proposed (Xiao et al.); however, whether they can improve clinical outcomes remains unclear. Similarly, although approaches such as personalized rTMS (Lee et al.) and novel DBS applications (Xu et al.) are intriguing, there are methodological challenges in the field of rehabilitation such as setting up placebo-controlled trials for device-based interventions. It is important to devise study designs that incorporate ethical and technical innovations to enable RCTs using cutting-edge methods.

Third, given that neurorehabilitation inherently addresses multifaceted functional recovery, implementing an integrated outcome assessment is challenging. In the PoCoRe study, a comprehensive evaluation, including cognitive and psychological aspects, was conducted (Jöbges et al.), but many studies have focused only on physical function metrics. Future research should enhance outcome assessment frameworks by including holistic outcomes such as patients' degree of community reintegration, quality of life, and psychological health (Wu and Jin). For example, it is important to take a multifaceted perspective on rehabilitation effects, examining, for instance, the extent to which improvements in dexterity or muscle strength ultimately increase independence in daily living, or whether they have ripple effects on cognitive function or motivation.

Furthermore, bridging the gap in clinical applications requires implementation research, i.e., research on methods to put evidence into practice. Even when an intervention is shown to be effective, there is insufficient insight on techniques to incorporate it into real-world rehabilitation programs in terms of training frequency and duration, staff education, and cost-effectiveness. It is hoped that more studies will include process evaluations of intervention implementation as seen in the HOME rehabilitation protocol in this Research Topic (Reeder et al.). As rehabilitation is highly context-dependent, comprehensive consideration, including environmental adjustments and organizational support, is required for translating research findings into practice.

Finally, human resource development and interdisciplinary collaboration are long-term issues. The utilization of cutting-edge technology and the promotion of personalized medicine require collaboration among rehabilitation professionals, engineers, neuroscientists, data scientists, and others (Li et al.; Liu et al.). Although studies on this Research Topic were conducted by multidisciplinary teams, further advancement through the establishment of interdisciplinary research centers and promotion of international collaborative projects is expected to accelerate innovation across the entire neurorehabilitation field.

5 Conclusion

The findings compiled in this Research Topic, titled "*Exploring evidence for neurorehabilitation advancements*," demonstrate that the field of neurorehabilitation is steadily accumulating scientific evidence and forging new frontiers in both therapeutic technologies and strategies. Rehabilitation, which often relies on experience and intuition, is now transforming into an optimized approach for each patient based on precise assessment and evidence. The insights from each paper pertain to specific disorders or interventions in isolation; however, collectively, they form part of a larger movement toward the ultimate goal of neurorehabilitation: maximizing patients' functional recovery and improving their quality of life.

Certainly, many challenges must be overcome before the best possible rehabilitation, which is truly supported by evidence, can be realized. However, the types of efforts highlighted in this Research Topic, i.e., meticulous reviews to assess the current state, bold applications of new technology, intervention designs based on patient-centered thinking, and research pursued with an international outlook, will help resolving each of these challenges. Neurorehabilitation is a field supported by the hope afforded by the plasticity of the human brain and nervous system. To ensure concrete outcomes, continued collaboration between researchers and clinicians and the pursuit of innovative research are required.

The insights presented in this Research Topic offer valuable guidance for future research and clinical practice. By using these findings as a starting point and by continuously exploring new questions and accumulating evidence, neurorehabilitation will further develop. We are confident that this will ultimately lead to a future in which individuals with disabilities can fully realize their abilities and lead fulfilled lives. Through this Editorial, we hope that readers will, in their own capacities, contribute to the advancement of neurorehabilitation and share this vision for the future.

Author contributions

HN: Writing – review & editing, Writing – original draft. AM: Writing – review & editing. TI: Writing – review & editing. KO: Writing – review & editing. MS: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Critical review of the evidence for Vojta Therapy: a systematic review and meta-analysis

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Introduction: It is essential to link the theoretical framework of any neurophysiotherapy approach with a detailed analysis of the central motor control mechanisms that influence motor behavior. Vojta therapy (VT) falls within interventions aiming to modify neuronal activity. Although it is often mistakenly perceived as exclusively pediatric, its utility spans various functional disorders by acting on central pattern modulation. This study aims to review the existing evidence on the effectiveness of VT across a wide range of conditions, both in the adult population and in pediatrics, and analyze common therapeutic mechanisms, focusing on motor control modulation.

Aim: The goals of this systematic review are to delineate the existing body of evidence concerning the efficacy of Vojta therapy (VT) in treating a broad range of conditions, as well as understand the common therapeutic mechanisms underlying VT with a specific focus on the neuromodulation of motor control parameters.

Methods: PubMed, Cochrane Library, SCOPUS, Web of Science, and Embase databases were searched for eligible studies. The methodological quality of the studies was assessed using the PEDro list and the Risk-Of-Bias Tool to assess the risk of bias in randomized trials. Methodological quality was evaluated using the Risk-Of-Bias Tool for randomized trials. Random-effects meta-analyses with 95% CI were used to quantify the change scores between the VT and control groups. The certainty of our findings (the closeness of the estimated effect to the true effect) was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE).

Results: Fifty-five studies were included in the qualitative analysis and 18 in the meta-analysis. Significant differences in cortical activity ($p = 0.0001$) and muscle activity ($p = 0.001$) were observed in adults undergoing VT compared to the control, as well as in balance in those living with multiple sclerosis ($p < 0.03$). Non-significant differences were found in the meta-analysis when evaluating gross motor function, oxygen saturation, respiratory rate, height, and head circumference in pediatrics.

Conclusion: Although current evidence supporting VT is limited in quality, there are indications suggesting its potential usefulness for the treatment of respiratory, neurological, and orthopedic pathology. This systematic review and meta-analysis show the robustness of the neurophysiological mechanisms of VT, and that it could be an effective tool for the treatment of balance in adult neurological pathology. Neuromodulation of motor control areas has been confirmed by research focusing on the neurophysiological mechanisms underlying the therapeutic efficacy of VT.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=476848, CRD42023476848.

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meta-analysis, Vojta therapy, systematic review, neurorehabilitation, neurophysiotherapy, reflex locomotion therapy

1 Introduction

To obtain a comprehensive understanding of any neurophysiotherapy approach, it is imperative to align its theoretical framework with a thorough exploration of the underlying motor control mechanisms regulating motor behavior (1). Additionally, clinical improvements in motor behavior must be quantified by functional outcomes ranging from performance (activities, participation) to capacities observed in a standardized environment and changes in body functions (2, 3) (muscle strength, kinematics). Vojta therapy (VT) can be classified within the domain of interventions aimed at neuromodulation by influencing nervous activity using directed physical, chemical, tactile, or mechanical stimulation. Under this paradigm, Vojta therapy is a therapeutic tool based on the neurophysiological principles of motor and postural control. It has been a therapeutic approach in continuous development since its inception in the 1960s to the present day. Vojta therapy uses tactile and proprioceptive sensory stimulation to activate innate locomotion complexes in humans known as "innate patterns."

The stimulation is performed in a defined starting position (Reflex Rolling in the supine and side lying position, and reflex creeping from the prone position), both postures activating coordinated muscle activation, including axial elongation of the spine, and automatic postural control. These interventions specifically target designated areas in the central nervous system (CNS), resulting in the modulation of the excitability and firing patterns of neuronal circuits (4).

Although previous systematic reviews tried to understand the evidence of VT in pediatric population and in specific cohorts such as cerebral palsy (5) or specific body functions (2, 6, 7), no systematic review has studied the evidence of this approach according to its therapeutic effects in both motor behavior and motor control (1). This review is the first to encompass studies with clinical evidence in adults: orthopedics and neurology, as well as studies with clinical evidence in pediatrics: respiratory, neurology, and non-neurological disorders, specifically addressing pediatric neurological and orthopedic alterations.

Previous revisions in respiratory function concluded from indicating VT as the most appropriate technique, among those analyzed, to intervene premature infants with respiratory dysfunction such as respiratory distress syndrome (6) to influencing blood gas, diaphragm movements, and functional respiratory parameters in patients with neuromotor disorders (7). VT has been included within the second of three levels of evidence in interventions for cerebral palsy (5). Poor study design has cast a shadow over the positive results in previous studies about VT, including lack of random sequence generation, concealed allocation, study blinding, incomplete outcome data collection, and selective reporting (8).

VT is frequently misconceived as a technique exclusively designed for pediatric applications, primarily attributed to its comprehensive understanding of the neuro-kinesiology of the ontogenetic development of human posture and movement. Its significant contribution to knowledge in this domain often leads to the oversight of its potential applicability across a diverse spectrum of disorders of body functions through the neuromodulation of central locomotor patterns or synergies. Consequently, the primary aim of this systematic review is to delineate the existing body of evidence concerning the efficacy of VT in treating a broad range of conditions. This involves the meta-analysis of measured outcomes within the International Classification of Functioning, Disability, and Health (ICF) framework to improve comprehensibility. The second goal is to compile evidence regarding the common therapeutic mechanisms underlying VT's effectiveness across diverse pathologies, with a specific focus on the neuromodulation of motor control parameters.

2 Methods

2.1 Data source and search methods

Guidelines from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement were consulted to develop this systematic review (9). The computerized databases Medline (PubMed), SCOPUS, Embase, Cochrane Library, and Web of Science were used to search for relevant studies. Keywords referring to the intervention were used, combined with Boolean operators (the complete search strategy is shown in Appendix A).

Searches were performed between 11 November 2023 and 11 December 2023 (from the date of inception of each database) using a combination of controlled vocabulary (i.e., medical subject headings) and free-text terms. Search strategies were modified to meet the specific requirements of each database. Searches of the reference lists of the included studies and previously published systematic reviews were also conducted.

This meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration no. CRD42023476848).

2.2 Criteria for considering studies and study selection

We used the Population, Intervention, Comparison, Outcomes, Time, and Study design (PICOTS) as a framework to formulate eligibility criteria (10).

2.3 Population

Any healthy population group or with any pathology.

2.4 Intervention

VT alone or combined with other therapy.

2.5 Comparison

Control group, placebo group, or sham group.

2.6 Outcomes

Any measurement variable related to the effects of Vojta therapy.

2.7 Time

No temporal restrictions were applied to the duration of the intervention or outcome measures. No filters were applied by the publication date.

2.8 Studies

Only interventional trials.

2.9 Inclusion criteria

All types of VT intervention studies were included in any type of cohort. VT should be carried out within an interventional group only or in comparison with a control group, another intervention, a placebo or a sham group.

2.10 Exclusion criteria

Systematic reviews, intervention protocols, studies on the degree of satisfaction or quality of life of families of children with disabilities, single-group intervention studies with combined treatment (not just Vojta), articles about a single case, articles on diagnostic system according to Vojta, congress communications, poster communications, full test not found, literature reviews, and articles with non-specified outcomes were excluded from this study.

2.11 Data extraction

First, two blinded investigators (JLSG and VNL) examined the studies obtained from the databases by screening by title and abstract according to the established inclusion criteria. In the case of discrepancies, a third investigator (MMP) intervened. After this first screening, the selected articles were read full text to understand if they met the criteria and could be included in the analysis. The authors of the included studies were contacted by e-mail with the aim of accessing possible unclear data. If no response was received, the data was excluded from the analysis.

2.12 Risk of bias and assessment of methodological quality of the studies

Two reviewers independently assessed the risk of bias in the studies (VNL and JLSG).

A revised tool to assess the risk of bias in randomized clinical trials (RoB2) (11) was used to assess the risk of bias in randomized trials. The tool is structured into five domains through which bias could be introduced into the outcome. These were identified based on empirical evidence and theoretical considerations. Because the domains cover all types of bias that may affect the results of randomized trials, each domain is mandatory, and no additional domains should be added. The five domains for individually randomized trials (including crossover trials) are: bias arising from the randomization process (D1); bias due to deviations from intended interventions (D2); bias due to missing outcome data (D3); bias in the measurement of the outcome (D4); and bias in the selection of the reported result (D5).

In addition, methodological quality was evaluated using the PEDro list (12), which assesses the internal and external validity of a study and consists of 11 criteria: (1) specified study eligibility criteria; (2) random allocation of subjects; (3) concealed allocation; (4) measure of similarity between groups at baseline; (5) subject blinding; (6) therapist blinding; (7) assessor blinding; (8) fewer than 15% dropouts; (9) intention-to-treat analysis; (10) between-group statistical comparisons; and (11) point measures and variability data. The methodological criteria were scored as follows: yes (one point), no (zero points), or unknown (zero points). The PEDro score of each selected study provided an indicator of the methodological quality (9–10 = excellent; 6–8 = good; 4–5 = fair; 3–0 = poor) (13).

Studies with research designs other than RCT are, by nature, at high risk of bias, and no formal quality appraisal was undertaken. Uncertainties and disagreements between reviewers were resolved in team discussions.

2.13 Overall quality of the evidence

The overall quality of the evidence was based on the classification of the results into levels of evidence according to the Grading of Recommendations Assessments, Development, and Evaluation (GRADE), which is based on five domains: (1) study design; (2) imprecision; (3) indirectness; (4) inconsistency; and (5) publication bias.

Evidence was categorized into the following four levels accordingly: (a) High quality: further research is very unlikely to change our confidence in the estimate of effect, all five domains are also met; (b) Moderate quality: further research is likely to have an important impact on our confidence and might change the estimate of effect, one of the five domains is not met; (c) Low quality: further research is very likely to have an important impact on our confidence and is likely to change the estimate of effect, two of the five domains are not met; and (d) Very low quality: any estimate of effect is very uncertain, three of the five domains are not met (14, 15).

2.14 Data synthesis and analysis

The meta-analysis was conducted utilizing Review Manager statistical software (version 5.4; Cochrane, London, UK). For the quantitative evaluation, effects were determined by computing standardized mean differences (SMD) and standard deviations for the alteration scores from before the intervention to after the intervention. In this process, the number of samples, the mean discrepancy, and the standard deviations (SDTs) for each group were gathered. In cases where the study only disclosed median and first- and third-quartile values, these were transformed into means and SDTs (16). In instances where the authors only provided standard errors, these were transformed into SDTs. If the study did not display the results, the authors reached out to obtain them; if the results were not accessible in this format, the means and SDTs were approximated from graphs (Image J program; National Institute of Health in Bethesda, Maryland, USA). If all these methods were unfeasible, the study was omitted from the quantitative analysis, and the data were exhibited in a qualitative manner.

In the case where the study did not disclose the mean difference between pre- and post-intervention in each group, the mean difference was derived using the values before and after the intervention. If the SDT of the difference was not provided, it was inferred from other data mentioned in the study: (1) utilizing other metrics reported in the study (for instance, confidence intervals and *p*-values, adhering to the principles outlined in Chapter 6.5.2.2 of the Cochrane Handbook) (17); or, if this was unattainable; (2) employing the correlation coefficient of the most analogous study included (adhering to the principles outlined in Chapter 6.5.2.8 of the Cochrane Handbook) (17); or if that was unattainable; (3) utilizing a conservative correlation coefficient of 0.5 (18). This methodology has been implemented in other meta-analyses (19, 20).

A meta-analysis was performed for each different application of VT. In each type of application, an analysis of the different conditions evaluated was performed: effects of VT on adults: neurophysiological tests (muscle activity and cortical activity) and adults with neurological diseases (balance); effects of VT on pediatrics: children with respiratory disorders (SpO_2 and respiratory rate); pediatric patients with non-neurological disorders (orthopedic disorders); pediatric patients with neurological disorders (gross motor function). Subgroup analyses were performed for the different scales used in the different primary outcome measures (for example, in the outcome measures of balance in adults with neurological disorders, balance was assessed with different tests such as the Timed Up and Go, the Berg Balance Scale, or the tandem test, and a subgroup analysis was performed for each different scale).

Meta-analysis was performed using the inverse variance method and a random-effects model with 95% confidence intervals, as it provides more conservative results in case of heterogeneity between studies. *p*-values <0.05 were considered statistically significant. An effect size (SMD) of 0.8 or greater was considered large, an effect size between 0.5 and 0.8 was considered moderate, and an effect size between 0.2 and 0.5 was considered small.

A sensitivity analysis was performed to evaluate the results. For this purpose, the meta-analysis was performed only with studies with low RoB and then without studies that imputed the SD value of the difference with a correlation coefficient estimated from another study or with a correlation coefficient of 0.5. The sensitivity analysis was conducted when the analysis could be performed in at least five studies. Study heterogeneity was assessed by the degree of between-study inconsistency (I^2). The Cochrane group has established the following interpretation of the I^2 statistic: 0–40% may not be relevant/important heterogeneity, 30–60% suggests moderate heterogeneity, 50–90% represents substantial heterogeneity, and 75–100% represents considerable heterogeneity (21). Skewness was assessed using funnel plots. These analyses were performed only if the subgroups had at least three studies.

2.15 Inter-rater reliability

Inter-rater reliability for screening, risk of bias assessment, and quality of the evidence rating were assessed using percentage agreement and Cohen's kappa coefficient (22). There was strong agreement between reviewers for the screening records and full texts (94.12% agreement rate and $k = 0.84$), the risk of bias assessment (98.19% agreement rate and $k = 0.96$), and the quality and strength of the evidence assessment (99.27% rate and $k = 0.98$).

3 Results

3.1 Study selection

Electronic searches identified 891 potential studies for review. After eliminating duplicates, a total of 567 studies remained. A total of 324 studies were excluded based on their titles/abstracts, leaving 113 articles for full-text analysis. Another 58 were excluded for inadequate design, population, intervention, results, and type of publication. Finally, 55 studies were included in the qualitative analysis, and 18 were included in the quantitative analysis. The entire selection process is shown in the PRISMA flow diagram (Figure 1).

3.2 Characteristics of included studies

The studies included in this review have been divided into different thematic areas: studies related to neurophysiological evidence; studies with clinical evidence in adults: orthopedics and neurology; and studies with clinical evidence in pediatrics: respiratory, neurology, and

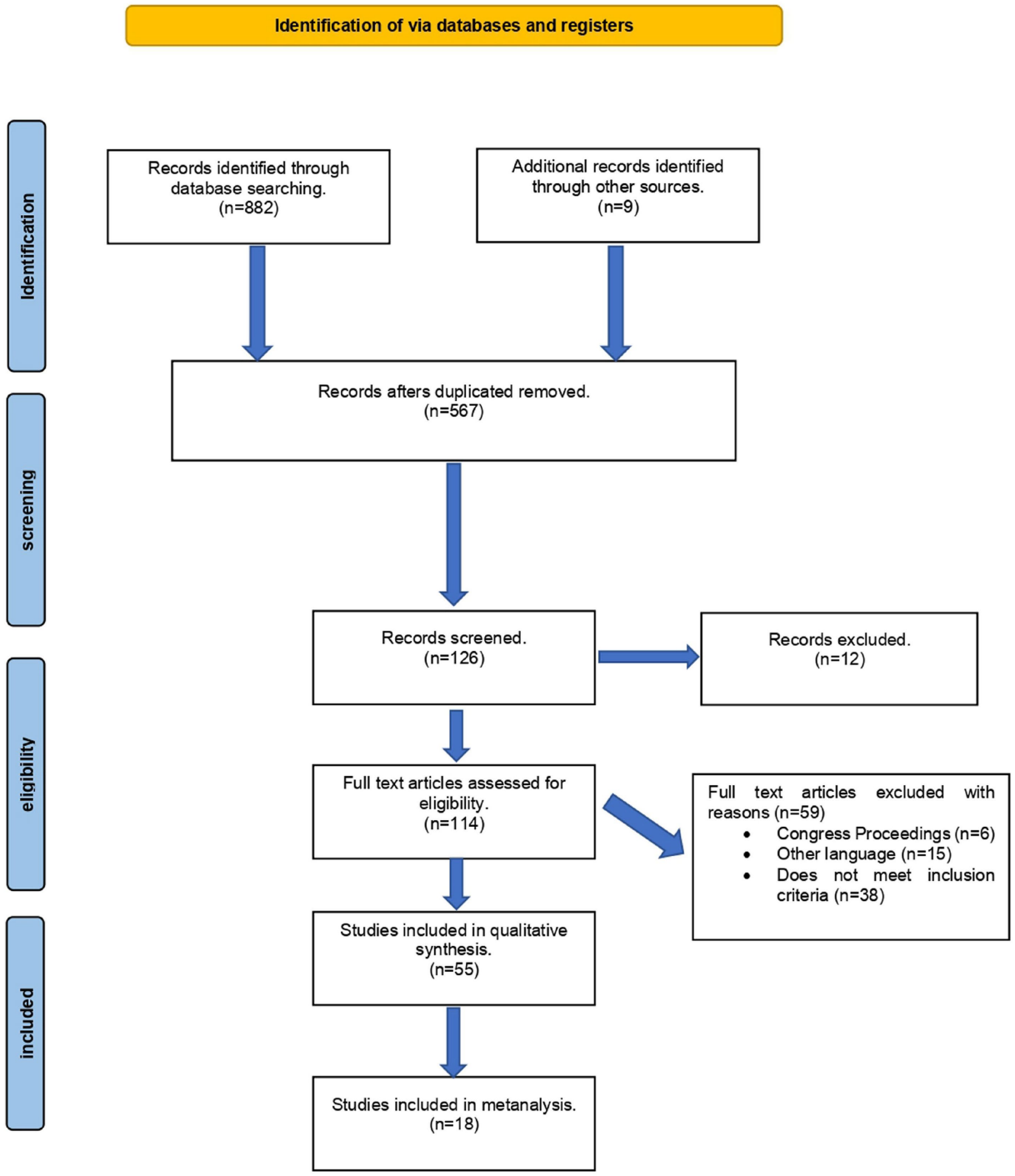

FIGURE 1
Complete search process flowchart. From Moher et al. (23).

non-neurological disorders. The characteristics of the intervention protocols of the VT groups are detailed in the Supplementary material.

3.3 Characteristics of included studies in neurophysiological evidence

Table 1 shows the main characteristics of the included studies. Sixteen studies were included in the qualitative analysis. All studies were intervention studies: 11 randomized controlled trials and five non-randomized clinical trials. These studies were conducted in Spain (24, 26–28, 33, 37, 38), Poland (25, 31, 35, 36) and the Czech Republic (29, 30, 32, 34, 39, 40). A total of 534 participants were included, including both men and women. The main measurement variables related to the neurophysiological evidence of VT were: muscle activity (24, 31, 33, 37), cortical activity (26, 27, 33, 39), subcortical activity (28–30, 34), concentration of free cortisol (25), cardiac autonomic control and respiratory rate (32), microcirculation properties of

TABLE 1 Characteristics of included studies in neurophysiological evidence.

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Pérez-Robledo et al., 2022 (24)	RCT	Healthy adults	Vojta group EG (27) Control group CG (27)	Vojta therapy The subjects were stimulated in areas not described by the Vojta methodology (distal third of the quadriceps and 8 cm cranial to the superior angle of the patellar bone)	Muscular activity (EMG)	Regarding muscular electrical activity, statistically significant differences were determined in all muscles during right-sided stimulation in the experimental group ($p < 0.001$), but not in the control group
Kiebzak et al., 2021 (25)	CT	Infants with Central Coordination Disorders	Vojta group EG (35)	Vojta therapy	Concentration of free cortisol in saliva	The cortisol measurement performed directly after rehabilitation showed above-normative values in three children. In the third measurement, all of the children presented a decreased concentration of free cortisol.
Sanz-Esteban et al., 2021 (26)	RCT	Healthy adults	Vojta group EG (20) Control group CG (20)	Vojta therapy The subjects were stimulated in areas not described by the Vojta methodology (distal third of the quadriceps and 8 cm cranial to the superior angle of the patellar bone)	Cortical activity (EEG)	The EG showed statistically significant differences in the theta, low alpha, and high alpha bands, bilaterally in the supplementary motor (SMA) and premotor (PMA) areas (BA6 and BA8), superior parietal cortex (BA5, BA7), and the posterior cingulate cortex (BA23, BA31). For the EG, all frequency bands presented an initial bilateral activation of the superior and medial SMA (BA6) during the first minute. This activation was maintained until the fourth minute. During the fourth minute, the activation decreased in the three frequency bands. From the fifth minute, the activation in the superior and medial SMA rose again in the three frequency bands.
Sanz-Esteban et al., 2021 (27)	RCT	Healthy adults	Vojta group EG (20) Control group CG (20)	Vojta therapy CG received a continuous sham stimulus on the thigh during the next 8 min	Muscular activity (EMG) and cortical activity (EEG)	Statistically significant differences were shown between the sham and experimental groups. EG participants were subjected to cluster analysis based on their muscle activation patterns, generating three different models of activation. Differences in the previous resting cortical activity in the left superior frontal area were found between clusters that activated limb muscles and the clusters that did not.
Sanz-Esteban et al., 2018 (28)	RCT	Healthy adults	Vojta group EG (12) Control group CG (4)	Vojta therapy The subjects were stimulated in areas not described by the Vojta methodology (distal third of the quadriceps and 8 cm cranial to the superior angle of the patellar bone)	Subcortical activity fMRI	Differences between groups showed greater activation in the right cortical areas (temporal and frontal lobes), subcortical regions (thalamus, brainstem, and basal nuclei), and the cerebellum (anterior lobe). EG had specific different brain activation areas, such as the ipsilateral putamen.

(Continued)

TABLE 1 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Hok et al., 2019 (29)	RCT	Healthy adults	Vojta group EG (30)	Vojta therapy	Subcortical activity fMRI	In direct voxel-wise comparison, heel stimulation was associated with significantly higher activation levels in the contralateral primary motor cortex and decreased activation in the posterior parietal cortex. Thus, we demonstrate that manual pressure stimulation affects multiple brain structures involved in motor control and the choice of stimulation site impacts the shape and amplitude of the blood oxygenation level-dependent response.
			Control group (30)	The protocol followed was the same, the only thing that changed was the activation zone: a control site at the right lateral ankle.		
Hok et al., 2017 (30)	RCT	Healthy adults	Vojta group EG (30)	Vojta therapy	Subcortical activity fMRI	Sustained pressure stimulation of the foot is associated with differential short-term changes in hand motor task-relate activation depending on the stimulation.
			Control group (30)	The protocol followed was the same, the only thing that changed was the activation zone: a control site at the right lateral ankle.		
Gajewska et al., 2018 (31)	CT	Healthy adults	Vojta group EG (25)	Vojta therapy	Muscular activity (EMG)	Following acromion stimulation, muscle activation was mostly expressed in the contralateral rectus femoris, rather than the contralateral deltoid and the ipsilateral rectus femoris muscles. After stimulation of the lower femoral epicondyle, the following order was observed: contra lateral deltoid, ipsilateral deltoid, and the contralateral rectus femoris muscle.
Opavsky et al., 2018 (32)	RCT	Healthy adults	Vojta group EG (28)	Vojta therapy	Cardiac autonomic control and Respiratory rate assessment	The active stimulation was perceived as more unpleasant than the control stimulation. Heart rate variability parameters demonstrated almost identical autonomic responses after both stimulation types, showing either modest increase in parasympathetic activity, or increased heart rate variability with similar contributions of parasympathetic and sympathetic activity. Heart rate and respiration rate decreased after both active and control stimulations.
			Control group (28)	Pressure on the lateral ankle (control), in an area not included among the active zones used by Vojta therapy		
Sánchez-González et al., 2023 (33)	RCT	Healthy adults	Vojta group EG (14)	Vojta therapy	Muscular activity (EMG) and cortical activity (fNIRS)	In relation to the oxygenated hemoglobin concentration (HbO), an interaction between the stimulation phase and group was observed. Specifically, the Vojta stimulation group exhibited an increase in concentration from the baseline phase to the first resting period in the right hemisphere, contralateral to the stimulation area. This rise coincided with an enhanced wavelet coherence between the HbO concentration and the electromyography (EMG) signal within a gamma frequency band (very low frequency) during the first resting period
			Control group (13)	The subjects were stimulated in areas not described by the Vojta methodology (distal third of the quadriceps and 8 cm cranial to the superior angle of the patellar bone)		

(Continued)

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TABLE 1 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Martínek et al., 2022 (39)	CT	Healthy adults	Vojta group EG (17)	Vojta therapy	Cortical activity (EEG)	The analysis found statistically significant differences in the frequency bands alpha-2, beta-1, and beta-2 between the condition prior to stimulation and the actual stimulation in BAs 6, 7, 23, 24, and 31 and between the resting condition prior to stimulation, and the condition after the stimulation was terminated in the frequency bands alpha-1, alpha-2, beta-1, and beta-2 in BAs 3, 4, 6, and 24
Řasová et al., 2021 (40)	RCT	Adults with multiple sclerosis	Motor program activating therapy (42)	Participants underwent 16 face-to-face sessions (1 h, twice a week for 2 months). They were corrected into a postural position where the joints were functionally centered. Then somatosensory (manual and verbal) stimuli were applied to activate motor programs in the brain, which then led to the cocontraction of the patient's whole body when lying, sitting, standing up, or moving forward.	Subcortical activity (fMRI)	No statistically significant change in the whole statistic skeleton was observed (only a trend for decrement of fractional anisotropy after Vojta's reflex locomotion). Additional exploratory analysis confirmed significant decrement of fractional anisotropy in the right anterior corona radiata.
			Vojta group EG (29)	Vojta therapy		
			Functional electric stimulation (21)	Participants first underwent individual 2-h session consisting of postural correction. Then patients received the device to be used as much as they felt able to during their normal daily activities. After 14 days, the patients received the second individual 2-h session and underwent 1-h postural correction. The patients then continued to use the device daily for the next 6 weeks.		
Prochazkova et al., 2021 (34)	RCT	Adults with multiple sclerosis	Motor program activating therapy (18)	Patients are corrected into a postural position where the joints are functionally centered. Then somatosensory (manual and verbal) stimuli were applied to activate motor programs in the brain, which then lead to the cocontraction of the patient's whole body when the patient is lying, sitting, standing up, or moving forward.	Subcortical activity (fMRI)	Physiotherapy in pwMS leads to extension of brain activity in specific brain areas (cerebellum, supplementary motor areas, and premotor areas) in connection with the improvement of the clinical status of individual patients after therapy ($p = 0.05$). Greater changes ($p = 0.001$) were registered after MPAT than after VRL. The extension of activation was a shift to the examined activation of healthy controls, whose activation was higher in the cerebellum and secondary visual area ($p = 0.01$).
			Vojta group EG (20)	Vojta therapy		

(Continued)

TABLE 1 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Ptak et al., 2022a (35)	CT	Healthy infants	Vojta group EG (22)	Vojta therapy	Microcirculation properties of muscles (Thermovision method)	In the study group, changes in the microcirculation parameters of the extensor muscles of the back occurred immediately after the therapy at the first examination.
Ptak et al., 2022b (36)	CT	Healthy children	Group with children with increased muscle tone (IMT) (11)	One-time Vojta therapy session, which was continued for 4 weeks by parents at home.	Frequency Stiffness Elasticity Relaxation, Creep of the erector spinae. (The MYOTON device by Myoton AS Estonia)	Changes in the viscoelastic parameters of the extensor muscles of the back occurred immediately after the therapy at the first examination. Whereas changes in the supporting and extensor function of the limbs occurred in both groups at the second examination.
			Group with children with non-increased muscle tone (nonIMT) (11)			
Perales-López et al., 2013 (37)	RCT	Healthy adults	Manual group (45)	First phase of VR is activated from a single point of stimulation, the pectoral area.	Muscular activity (EMG)	There are significant contradictions in both types of intervention regarding resting levels $p = 0.00$. However, significant differences are not found in the main result between manual intervention or that produced by the mechanical mechanism $p = 0.29$. It was not possible to demonstrate significant differences, $p = 0.64$ in the activation stage with webcam
			Mechanic group (45)	The pectoral area is stimulated with a mechanical device.		
			Baseline group (45)	Baseline values are taken for all variables in the resting state in the starting position of the proposed exercise, without stimulation.		
			Online mechanic group (45)	Same as the mechanical group but supervised from a remote terminal		

RCT, randomized controlled trial; CT, clinical trial; EMG, electromyography; EG, experimental group; CG, control group; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; pwMS, people with multiple sclerosis.

muscles (36), and frequency stiffness, elasticity, relaxation, and creep of the erector spinae (35).

3.4 Characteristics of included studies in clinical evidence in adults

3.4.1 Characteristics of included studies on clinical evidence in adults with neurological disorders

Table 2 shows the main characteristics of the included studies. Eight studies were included in the qualitative analysis. All studies were intervention studies: five randomized controlled trials and three non-randomized clinical trials. These studies were conducted in Spain (45, 46), Germany (43), Thailand (44) and the Czech Republic (34, 40–42). A total of 381 participants were included, including both men and women. The main measurement variables related to the balance and postural control evidence of VT were: Berg Balance Scale (34, 40–42, 45, 46), test up and go (34, 40, 42, 44), the 12-item Multiple Sclerosis Walking Scale (MSWS-12) (40), Timed 25 Foot Walk (T25FW), Nine-Hole Peg Test (NHPT) (34), tandem test (6 m) (46), concentration of free cortisol and cortisone (41), 10-M walk test (46), Fatigue Severity Scale (45), Motor Evaluation Scale for Upper Extremity in Stroke Patients (MESUPES), and National Institute of Health Stroke Score (NIHSS) (43).

3.4.2 Characteristics of the included studies on adults with orthopedic disorders

Table 3 summarizes the main features of the included studies. Four studies were included in the qualitative analysis. Interventional studies included two randomized controlled trials and two non-randomized clinical trials.

These studies were conducted in South Korea (47), Spain (48, 49), Poland (50), and Romania (51).

A total of 180 participants included both men and women. The main measurement variables related to improvements in postural control, functionally, disability, and pain of VT were: the thickness of the abdominal muscles, the area of the diaphragm during inspiration and expiration (47), pain intensity (48, 49, 51), range of motion and strength, quality of life (48, 51), disability, flexibility, and radiculopathy (49), and gait parameters (50).

TABLE 2 Characteristics of included studies on clinical evidence in adults with neurological disorders.

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Angelova et al., 2020 (41)	RTC	Adults with multiple sclerosis	Control group (CG) (18) Motor program activating therapy (MPAT)	They were corrected into a different ontogenesis position. Somatosensory (manual and verbal) stimuli were applied to activate motor programs in the brain. The patient's whole body when the patient was lying, sitting, standing up, or moving forward.	Serum level of cortisol, cortisone, 7 -OH-DHEA, 7-OH-DHEA, 7-oxo-DHEA, Paced Auditory Serial Addition Test (PASAT) Impact of MS by (MSIS) Berg Balance Scale (BBS)	The effect of therapy regardless of the group was significantly improved in cognitive functions measured by PASAT. This condition further improved after the next 2 months. After passing the MSIS scale, there was an improvement in the impact of multiple sclerosis. Following this improvement, a decrease in the median of 7-oxo-DHEA was observed. There was a significant difference between the groups in the change of balance measured by the BBS score (while Group 1 improved by 1 point, Group 2 worsened) Vojta's reflex locomotion had a higher impact on neuroactive steroids. It led to an immediate significant decrement in cortisone, 7-OH-DHEA, and 7-oxo-DHEA while hardly any change was observed following motor program activating therapy. Deference's between groups were statistically significant [cortisone ($p = 0.0223$), 7-OH-DHEA ($p = 0.0232$) and 7-oxo-DHEA ($p = 0.0053$)] After Vojta therapy activation, cortisone, 7α-OH-DHEA, and 7-oxo-DHEA decreased significantly. The MPAT group did not obtain significant changes (increases in DHEA).
			Experimental group (EG) (14) Vojta group (VG)	Vojta therapy		
Řasová et al., 2021 (40)	RTC	Adults with multiple sclerosis	MPAT (42)	All groups underwent 2-month ambulatory neurofacilitation PT. Participants underwent 16 face-to-face sessions (1 h, twice a week for 2 months). They were corrected into a postural position where the joints were functionally centered. Then somatosensory (manual and verbal) stimuli were applied to activate motor programs in the brain, which then led to the cocontraction of the patient's whole body when lying, sitting, standing up, or moving forward.	The balance Berg Balance Scale [BBS] Timed Up and Go (TUG) 12-item Multiple Sclerosis Walking Scale [MSWS-12] MS impact with the 29-item Multiple Sclerosis Impact Scale [MSIS-29]. Fractional anisotropy (FA) Global FA White matter integrity: magnetic resonance imaging on a 3Tmagnetic resonance scanner	No statistically significant change in the whole statistic skeleton was observed (only a trend for decrement of fractional anisotropy after Vojta's reflex locomotion). Additional exploratory analysis confirmed significant decrement of fractional anisotropy in the right anterior corona radiata. A significant improvement of Balance measured by BBS was followed by a decrement of FA in the right anterior corona radiata. No global FA change was detected. Treatment effect. MPAT showed the highest effect on clinical outcomes, with the improvement of BBS VT was associated with the strongest FA change, global FA FA changes among the treatment groups in the left stria terminalis and right superior longitudinal fasciculus
			EG (29) Vojta group	Vojta therapy		
			Functional Electrical Stimulation (FES) (21)	Participants first underwent individual 2-h session consisting of postural correction. Then patients received the device to be used as much as they felt able to during their normal daily activities. After 14 days, the patients received the second individual 2-h session and underwent 1-h postural correction. The patients then continued to use the device daily for the next 6 weeks.		

(Continued)

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TABLE 2 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Prochazkova et al., 2021 (34)	RCT	Adults with multiple sclerosis and control healthy group	MPAT (18)	They were corrected into a different ontogenesis position. Somatosensory (manual and verbal) stimuli were applied to activate motor programs in the brain. The patient's whole body when the patient was lying, sitting, standing up, or moving forward.	fMRI: subcortical activity Timed 25-foot walk [T25FW] Timed Up and Go (TUG) Berg Balance Scale (BBS) Nine-Hole Peg Test (NHPT) Paced Auditory Serial Addition Test (PASAT)	Physiotherapy in MS leads to extension of brain activity in specific brain areas (cerebellum, supplementary motor areas, and premotor areas) in connection with the improvement of the clinical status of individual patients after therapy Greater changes were registered after MPAT than after VT. The extension of activation was a shift to the examined activation of healthy controls, whose activation was higher in the cerebellum and secondary visual area. After analyzing the rest of the variables, there was no significant difference between MPAT and EG
			Vojta group EG (20)	Vojta therapy (VT)		
			Healthy group (HG)	Healthy volunteers underwent an fMRI examination that was considered to be a control.		
Lopez et al., 2021 (46)	Quasi-experimental	Adults with multiple sclerosis	Vojta group EG (12)	Vojta therapy.	Quantitative. Berg Balance Scale (BBS) Tandem test (6 m) 10 m Walk test.	Vojta group patients improved their rating significantly in the subsequent measurement to session 1 and remained at the last evaluation 2 weeks later. However, with the same test, the group (CG) did not improve Comparison between groups (last measurement versus initial evaluation) found significant differences. In the Tandem test and 10-meter Walk test variables, significant differences were found between the Vojta group and the control group.
			CG (9)	The program consisted of balance exercises targeting core stability, exercises of coordination, and Pilates as well as individual sessions using the Bobath concept. Patients in this group walked at least for 20 min per day during the study period.		
Carratalá-Tejada et al., 2022 (45)	Reversal design (Single-subject research)	Adults with multiple sclerosis	Experimental groups EG (23)	Three intervention periods: A Convencional therapy B Vojta therapy + Convencional therapy A Convencional therapy	Berg Balance Scale (BBS) Performance Oriented Mobility Assessment (POMA), the Fatigue Severity Scale (FSS) Instrumental analysis of the gait recorded by Vicon Motion System	Significant differences in balance using the BBS and the POMA after the RLT intervention. Significant improvements in the stride length and velocity after the RLT period

(Continued)

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TABLE 2 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Pavlikova et al., 2020 (42)	RCT	Adults with multiple sclerosis	CG (55)	Specific treatment of balance was restricted to a maximum of 10 min per session. In both IT-1 and IT-O cohorts, the patients underwent conventional exercises, including stretching, core stability, and light strengthening exercises. In CZ-O cohort, Vojta reflex locomotion treatment (CG) Balance-specific treatment was carried out in two IT centers and in the CZ-O. The treatment of the Intervention group consisted of at least 25 min of balance-specific treatment aimed at improving the participant's control of position and movement of the center of mass and body segments during static, dynamic, and transitional tasks.	Berg Balance Scale [BBS] Timed Up and Go (TUG)	The BBS Overall, the physiotherapy improved the static balance measured by BBS. There was no statistically significant difference in the overall improvement between countries. We observed a statistically significant mean difference favoring intervention (balance-specific) groups over the control. The TUG measurements were analyzed for the Czech and Italian outpatient cohorts due to a large proportion of missing data in the inpatient cohorts. The physiotherapy improved the dynamic balance measured by TUG Of the 91 patients, 27 (30%) patients improved in dynamic balance by 2 s or more. There was no statistically significant difference in the overall improvement between countries. We did not observe any statistically significant difference between intervention and control groups the percentage of improved patients did not differ between control and intervention groups.
			EG (94)	Patients in both IT-1 and IT-O cohorts underwent Sensory-Motor Integration Training (SMIT) Patients in CZ-O cohort underwent Motor Program Activating therapy (MPAT)		
Epple et al., 2020 (43)	RCT	Stroke patients	Vojta group EG (19)	Vojta therapy and afterward were mobilized with gait training, if feasible.	Trunk control test (TCT) National Institute of Health Stroke Scale (NIHSS) Catherine Bergego Scale (CBS) Motor Evaluation Scale for Upper Extremity in Stroke Patients (MESUPES) Barthel Index (BI)	treatment with Vojta therapy was beneficial in the early rehabilitation of acute stroke patients with a severe hemiparesis within 72 h after onset showing improved postural control, degree of neglect, and motor function compared to standard physiotherapy, Vojta patients achieved a greater improvement in the MESUPES and the NIHSS than patients in the control group (20% vs. 10, and 9.5% vs. 4.8%, respectively) There was a trend showing greater improvement in the BI from baseline to day 9 in the Vojta group (17.5% in the Vojta group,10% in the control group)
			CG (18)	The control group received conventional physiotherapy which consisted of repetitive sensorimotor exercises using the existing function of the affected extremity in task-oriented training and movements used during daily activity, passive movements of the limbs, trunk strengthening exercises, goal-directed movements, and mobilization including gait training.		
Tayati et al., 2020 (44)	Quasi-experimental	Chronic stroke	Vojta group EG (20)	Vojta therapy	Timed Up and Go (TUG)	Average and median TUGT Friedman test demonstrated a significant difference between these three values. The median TUGT was Wilcoxon test showed significant difference of pre- versus post-treatment in every session.

RCT, randomized controlled trial; CT, clinical trial; EG, experimental group; CG, control group; MPAT, motor program activating therapy; VG, Vojta group; FES, functional electrical stimulation; HG, healthy group; MS, multiple sclerosis; fMRI, functional magnetic resonance imaging; TUGT, Timed Up and Go test; BI, Barthel Index; MESUPES, Motor Evaluation Scale for Upper Extremity in Stroke Patients; CBS, Catherine Bergego Scale; NIHSS, National Institute of Health Stroke Scale; TCT, Trunk Control Test; SMIT, Sensory-Motor Integration Training; BBS, Berg Balance Scale; FSS, Fatigue Severity Scale; POMA, Performance Oriented Mobility Assessment; MSIS-29, multiple sclerosis impact with the 29-item Multiple Sclerosis Impact Scale; MSWS-12, 12-item Multiple Sclerosis Walking Scale; PASAR, Paced Auditory Serial Addition Test; MSIS, Multiple Sclerosis Impact Scale; NHPT, Nine-Hole Peg Test; T25FW, timed 25-foot walk; FA, fractional anisotropy.

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3.5 Characteristics of included studies in clinical evidence in pediatrics

3.5.1 Characteristics of the included studies on children with neurological disorders

Table 4 summarizes the main features of the included studies. Nine studies were included in the qualitative analysis. Interventional studies included five randomized controlled trials and four non-randomized clinical trials. These studies were conducted in Turkey (54), South Korea (52, 53, 58), Thailand (57, 59), China (55), Romania (60), and Spain (56). A total of 267 participants were included, both men and women. The main measurement variables related to motor function, postural control, balance, functionality, degree of satisfaction, and quality of life of VT were: gross motor function measure with GMFM (52, 53, 55, 56, 59), and Alberta Infant Motor Scale (AIMS) (54), trunk control (53), balance (60), weight-bearing distribution (58, 60), range of motion (59), gait analysis (58, 60), Timed Up and Go (TUG) six-minute walking test (6MWT) (57), parents emotional status (54), parents quality of life (54) and parents satisfaction (59).

3.5.2 Characteristics of the included studies in pediatrics with non-neurological disorders

Table 5 summarizes the main features of the included studies. Nine studies were included in the qualitative analysis. Interventional studies included six randomized controlled trials and three non-randomized clinical trials.

These studies were conducted in Spain (61, 67), Poland (35, 62, 64, 68), Germany (63, 65), and Norway (66). A total of 691 participants were included, both men and women. The main measurement variables related to bone mineralization, anthropometry, stress and pain, spine and head alignment, plagiocephaly, functionality, and weaning of VT were: Bone mineralization (61), anthropometric measurements (61, 67), bone formation and resorption measured, not painful or not stressful (67), three-dimensional trunk parameters (62), angle of trunk rotation (68), the myotonometric measurement of the erector spinae (35), cranial vault asymmetry (63), joint motion ranges and manual skills (64), restriction in head rotation and convexity of the spine (65), and weaning from nasogastric feeding (66).

3.5.3 Characteristics of the included studies in pediatrics with respiratory disorders

Table 6 summarizes the main features of the included studies. Eight studies were included in the qualitative analysis. Interventional studies included five randomized controlled trials and three non-randomized clinical trials.

These studies were conducted in South Korea (47, 52), India (70–72), Germany (73), Italy (69), and Egypt (74). A total of 276 participants were included, both men and women. The main measurement variables related to respiratory gasses, compliance, respiratory rate, stress, and pain of VT were: airflow and esophageal pressure (73), Gross Motor Function Measure (GMFM-88), and diaphragmatic movements in inspiration and expiration (52), oxygen saturation ($SatO_2$) (69–72, 74), transcutaneous carbon dioxide ($PtcCO_2$) transcutaneous oxygen ($PtcO_2$) (69, 71), arterial blood gas (PaO_2) (71) respiratory rate (69, 72, 74), the onset of stress or pain and risk of brain damage (69) and airway re-expansion pulmonaire (71).

3.6 Risk of bias

Due to the design of the included studies, all of them were analyzed using the RoB2.

3.6.1 Risk of bias in neurophysiological evidence studies

As assessed by RoB2, 40% (2/5) of the studies showed a low risk of bias, and 40% (2/5) showed some concerns. The items with some concerns were "Randomization process," in which 20% (1/5) and "Selection of the reported result," in which 20% (1/5).

3.6.2 Risk of bias in clinical evidence in adults with neurological disorder studies

As assessed by RoB2, 100% (4/4) of the studies showed a high risk of bias. The items with the highest risk of bias were "Randomization process," in which 40% (2/5), "Missing outcome data," in which 40% (2/5), and "Selection of the reported result," in which 20% (1/5).

3.6.3 Risk of bias in clinical evidence in pediatrics with respiratory disorders studies

As assessed by RoB2, 33% (1/3) of the studies showed a high risk of bias, and 67% (2/3) showed some concerns. The item with the highest risk of bias was "Randomization process," in which 33% (1/3).

3.6.4 Risk of bias in clinical evidence in pediatrics with neurological disorders studies

As assessed by RoB2, 25% (1/4) of the studies showed a high risk of bias, 50% (2/4) showed some concerns, and 25% (1/4) of the studies showed a low risk of bias. The item with the highest risk of bias was "Randomization process," in which 25% (1/4).

3.6.5 Risk of bias in clinical evidence in studies in pediatrics with non-neurological disorders

As assessed by RoB2, 100% (2/2) of the studies showed a low risk of bias.

Figure 2 summarizes the risk of bias of 50 selected studies, considering the main outcomes.

Risk of bias is represented as percentages among all included studies.

3.7 Methodological quality

All PEDRO scale scores can be found in Table 7.

3.7.1 Methodological quality of included studies in neurophysiological evidence

The methodological quality score ranged from 5 to 9 out of a maximum of 10 points. The mean methodological quality score of the included studies was 7.1. Most of the included studies had "good" methodological quality. The most frequent biases were related to therapist blinding. In the reliability analysis, the agreement between the two reviewers regarding the methodological quality of the included studies was excellent, according to the kappa coefficient ($k = 0.98$).

3.7.2 Methodological quality of included studies in clinical evidence in adults with neurological disorders

The methodological quality score ranged from 5 to 9 out of a maximum of 10 points. The mean methodological quality score of the included studies was 6.1. Most of the included studies had "good" methodological quality, and one of them was excellent. The most frequent biases were related to therapist blinding. In the reliability analysis, the agreement between the two reviewers regarding the methodological quality of the

TABLE 3 Characteristics of the included studies on adults with non-neurological disorders.

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Ha et al., 2016 (47)	RCT	Young healthy adults	Control group CG (7)	Arbitrary point in the same starting position as EG	The thickness of the muscles (EO), the (IO), the (TrA), and (RA) (ultrasonic image). The area of the diaphragm during inspiration and expiration (ultrasonography) The area of the diaphragm and the thickness were measured before stimulation and after 4 min of stimulation.	Vojta group: the thickness of the TrA and the diaphragm significantly increased during stimulation while the thickness of the EO significantly decreased in normal adults. Considerable change in the area of the diaphragm during inspiration and expiration in the Vojta group, but not in the CG.
			Vojta group EG (7)	Vojta therapy		
Juárez et al., 2021 (48)	RCT	Adult patients with Subacromial impingement syndrome (IS)	Control group CG (30)	Standard therapy (ST): Tens, kinesiotherapy, and cryotherapy	Pain intensity (VAS). Functionality joint range of motion (RoM) and strength The Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire and The Constant-Murley Scale (CMS) Quality of life measurements. QoL (SF-12) Health Survey	After the intervention, both groups showed statistically significant differences in visual analog scale, RoM, and strength, which were also seen 3 months after the intervention. Vojta group is more efficient in both the short and medium term in reducing pain, improving functionality, increasing articular RoM and strength, and offering a better quality of life in IS patients.
			Vojta group (30)	ST + Vojta therapy		
Juárez et al., 2020 (49)	CT	Adult patients diagnosed with lumbosciatica	Control group CG (6)	TENS	Pain (the Visual Analogical Scale (VAS) and the Oswestry questionnaire). The degree of disability (validated Spanish versions of the Oswestry and Roland-Morris questionnaires) Flexibility: (Schober Test and Finger-tips to Floor Test) Radiculopathy: (Lasegue maneuver)	Significant improvements were noted after both treatments in indices for pain, disability, and flexibility, with the exception of disability after TENS. Improvements in radiculopathy were only observed with Vojta. An overall decrease in scores obtained after Vojta was observed with respect to those obtained after CG in pain, back pain, leg pain, disability, and flexibility.
			Vojta group (6)	Vojta therapy		
Łozińska et al., 2019 (50)	CT	Adult patients with spinal low back pain	Vojta group (17)	Vojta therapy	Gait parameters BTS G-SENSOR, the wireless inertial measurement unit system for spatial and temporal gait analysis	The cadence decreased, and the duration of the right and left limb walk cycles increased. Vojta therapy may improve spatial and temporal gait parameters in adults with low back pain.

(Continued)

TABLE 3 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Iosub ME et al., 2023 (51)	CT	Adult patients with Lumbar disc herniation	Control group CG (39)	Conservative physiotherapy program (mobility and strength exercises and motor control exercises).	To determine the severity of pain (Visual Analog Scale (VAS)) To assess the functional status and indicate the limitation in everyday life activities (Oswestry Disability Index (ODI)) Mobility tests: finger-to-floor distance (FTF), trunk right lateral flexion (TRLF), trunk left lateral flexion (TLLF), and hip flexion (HF) testing. Muscle strength: (muscle strength trunk forward flexion (MSTFF), muscle strength trunk extension (MSTE), muscle strength trunk right lateral flexion (MSTRLF) and muscle strength trunk left lateral flexion (MSTLLF) Health-related quality of life (HRQL): (Nottingham Health Profile) (NHP) questionnaire).	Higher differences in pain intensity, disability level, mobility, strength, and health-related quality of life scores in both groups, but not between the groups. No significant differences in the examined parameters, with the exception of pain intensity, which dropped more in the Vojta therapy group than in only the conservative physical therapy group, although this was not significant.
			Vojta group (38)	Conservatory physical therapy program + Vojta therapy		

RCT, randomized controlled trial; CT, clinical trial; EG, experimental group; CG, control group; EO, external oblique abdominal; IO, internal oblique abdominal; TrA, transversus abdominis; RA, rectus abdominis; ST, standard therapy; RoM, range of motion; DASH, disabilities of the arm, shoulder, and hand; CMS, Constant–Murley scale; QoL (SF-12), Quality of life measurements; TENS, transcutaneous electrical nerve stimulation.

included studies was excellent, according to the kappa coefficient ($k = 0.98$).

3.7.3 Methodological quality of included studies in clinical evidence in adults within adults with orthopedic disorders

The methodological quality score ranged from 6 to 7 out of 10 points. The mean methodological quality score of the included studies was 6.5. All of the included studies had "good" methodological quality. The most frequent biases were related to therapy and patient blinding. In the reliability analysis, the agreement between the two reviewers regarding the methodological quality of the included studies was excellent, according to the kappa coefficient ($k = 0.98$).

3.7.4 Methodological quality of included studies in clinical evidence in pediatrics neurological disorders

The methodological quality score ranged from 8 to 9 out of 10 points. The mean methodological quality score of the included studies was 8.4. All of the included studies had "good" methodological quality, and it was "excellent" in two of them. The most frequent biases were related to therapy blinding. In the reliability analysis, the agreement between the two reviewers regarding the methodological quality of the included studies was excellent, according to the kappa coefficient ($k = 0.88$).

3.7.5 Methodological quality of the included studies in clinical evidence in pediatrics with non-neurological diseases

The methodological quality score ranged from 7 to 10 out of 10 points. The mean methodological quality score of the included studies was 8.6. All of the included studies had "excellent" methodological quality, and it was "good" in two of them. The most frequent biases were related to therapist blinding. In the reliability analysis, the agreement between the two reviewers regarding the methodological quality of the included studies was excellent, according to the kappa coefficient ($k = 0.90$).

3.7.6 Methodological quality of the included studies in clinical evidence in pediatrics with respiratory disorders

The methodological quality score ranged from 6 to 9 out of 10 points. The mean methodological quality score of the included studies was 7.8. All of the included studies had "good" methodological quality, and it was

TABLE 4 Characteristics of the included studies on children with neurological disorders.

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Ha et al., 2018 (52)	RCT	Children with spastic cerebral pals	Control group CG (5)	Trunk strengthening exercises and gait training.	Gross motor function (GMFM-88)	Significant improvements in sitting GMFM-88 dimension before and after intervention in the VT group.
			Vojta group EG (5)	Vojta therapy		
Ha et al., 2022 (53)	RCT	Infant children with genetic disorders/ central hypotonia	Control group CG (10)	Exercises for Trunk stabilization, pelvic control in a sitting, lower limb strengthening, and balance in sitting and standing.	Abdominal muscle thickness ultrasonography. Segmental Assessment of Trunk Control (SATCo) Trunk angle sagittal plane and Trunk Sway with Dartfish software program and video-recording; Gross Motor Function Measure-88 (GMFM-88)	Abdominal muscle thickness rates: EG was significantly thicker than CG post-intervention. The thickness changes (post–pre) were significantly higher in the EG than in CG. SATCo trunk angles pre-post: Static control sagittal plane larger angles in the EG vs. CG at T3, T11, L3. Reactive control control sagittal plane decreased EG vs. CG at L3, S1. Coronal plane only S1 decreased EG vs. CG.
			Vojta group EG (10)	Vojta therapy		
Kavlak et al., 2022 (54)	RCT	Down Syndrome aged between 0 and 2 years	CG-NDT (12)	Bobath-NDT	Alberta Infant Motor Scale (AIMS) Beck Depression Scale (parents) Nottingham Health Profile (Quality of life, Parents)	Motor development significantly changes before and after in both groups. No differences were found between groups when comparing baseline and after-treatment scores. Beck Depression Scale and Nottingham Health Profile (parents) positive statistical differences pre-post on both groups, with no differences between groups.
			Vojta Group EG (11)	Vojta therapy		
Li et al., 2007 (55)	CT	Children with Cerebral palsy	Vojta group (138)	Vojta therapy, Bobath-NDT, traditional Chinese medicine massage, and acupuncture.	GMFM-88	Significant differences in pre-post GMFM scores. Significant differences in the improvements of GMFM among the different developmental levels.

(Continued)

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TABLE 4 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Sanz-Mengibar et al., 2021 (56)	CT	Children with cerebral palsy between 0 and 18 months	Vojta group (16)	Vojta therapy	Acceleration values and rate of item acquisition of GMFM-88	Rate of acquisition of items and acceleration values significantly improved after the intervention.
Ungurenanu et al., 2022 (60)	CT	Children with cerebral palsy 3–11 years old	Vojta group (12)	Vojta therapy + NDT	Berg Balance scale Stabilimeter	Significant differences in pre- and post-intervention Berg Scores. Significant improvements in leg weight-bearing symmetry in standing, with small size effect.
Nipaporn et al., 2022 (59)	RCT	Children with CP, GMFCS IV and V.	Control group CG (12)	Functional training based on motor development to control head, trunk, and limbs. The home program to the parents. 60 min sessions. Twice a week, for 8 weeks + parents' home program twice a day for 20 min.	GMFM-88 total score and individual dimensions: (a) lying and rolling, (b) sitting, and (c) crawling Range of motion (ROM): hip, knee, and ankle joints 5-point Likert scale for parents' satisfaction	GMFM-88 total scores of both groups were significantly increased from the baseline. Dimension lying and rolling significantly greater improvement in the EG than in the CG. Significant improvements in EG in lying, rolling, and sitting, but not statistically significant in the crawling dimension. CG tended to improve but the difference was not statistically significant. No significant differences in CG in any dimension from the baseline. Significant increase ROM: bilateral hip flex, bilateral hip ext., left knee flex, and bilateral ankle dorsiflex in both groups. Improvements were not statistically significant for bilateral knee extension and bilateral ankle plantarflex in both groups. No data about significant differences between groups in ROM. Parent's satisfaction scores in both groups were 5 (100%)
			Vojta therapy EG (12)	Vojta therapy		
Phongprapapan et al., 2023 (57)	prospective case series	Post lower limb surgery of children with CP aged 3–13 years old, and GMFCS I, II, and III.	Vojta group (11)	Vojta therapy	Video gait analysis in a 20-m walkway: walking distance cadence, speed, stride length, stride time. Expanded timed get-up-and-go test (ETGUG) Six minutes walking test (6MWT)	Significant improvements pre- and post-intervention in 6MWT, ETGUG, cadence, velocity, stride length, and stride time at 6 months following corrective musculoskeletal surgery and postoperative VT. Multivariable multilevel linear regression analysis demonstrated that all outcomes significantly improved pre-post operation, but also during the 4 months post-op with VT only.

(Continued)

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TABLE 4 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Sung et al., 2020 (58)	RCT	Children with spastic CP and GMFCS I to III.	Control group CG (7)	Exercise including trunk strengthening exercise and gait training	Abdominal muscle thicknesses (ultrasound scan) Temporospatial gait parameters (GAITRite electronic walkway) Foot pressure distribution (GAITRite electronic walkway)	In the EG pre-post, significantly increased thickness of rectus anterior and external oblique, while transversus did not change. Stance time and step width were significantly decreased. However, single support % of cycle and functional ambulation profile were significantly increased. In the CG pre-post, significantly increased thickness of Ext Oblique but Trasversus was significantly decreased. Single support % of the cycle was significantly decreased. Between groups pre-post: Rectus Ant was significantly increased in the EG compared to CG comparison, as well as Swing time, single support % of cycle, and functional ambulation profile. Stance time and step width were significantly decreased compared to CG (more stability?). Rearfoot pressure was significantly increased while forefoot was significantly decreased compared to CG (more stability?).
			Vojta group EG (6)	Vojta therapy		

RCT, randomized controlled trial; CT, clinical trial; EG, experimental group; CG, control group; VT, Vojta therapy; CP, cerebral palsy; GMFCS, gross motor function classification system; GMFM-88, gross motor function measurement 88; SATCo, Segmental Assessment of Trunk Control; T, thoracic; L, lumbar; S, sacral; NDT, neurodevelopmental therapy; AIMS, Alberta Infant Motor Scale; ROM, range of motion; ETGUG, expanded timed get-up-and-go test; 6MWT, six-minute walking test.

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TABLE 5 Characteristics of the included studies on pediatrics with non-neurological disorders.

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Torró-Ferrero et al., 2022 (67)	RCT	Preterm infants	Control group (15)	Limb and core massages	Bone mineralization (tibial speed of sound TIBIAL-SOS) Measurements of weight, height, and head circumference	Significant differences among the groups in the Tibial-SOS in terms of the benefit to the Vojta group. The group with the best evolution is Vojta group, and the group with the worst evolution is CG. All the groups showed statistically significant improvements in weight, height, and head circumference. All the groups evolved equally in these terms.
			Vojta Group 1 (17)	Vojta therapy		
			Control Group 2 (14)	Passive movements with gentle joint compression (PMC)		
Torró-Ferrero et al., 2022 (61)	Multicenter RCT	Preterm infants	Control group CG (36)	Limb and core massages	Bone formation and resorption measured (serum and urine bone biomarkers) anthropometric measurements of weight, height, and head circumference consider intervention as not painful or not stressful. Neonatal Infant Pain Scale (NIPS)	Vojta therapy is significantly an effective treatment for increasing bone formation and growth in preterm infants. This fact may have a positive effect on the prevention of osteopenia in this population. Furthermore, Vojta therapy has been shown to be more effective than other Physical therapy modalities such as CG or EG2. NIPP results remained unmodified during the Vojta therapy.
			Vojta group EG1 (38)	Vojta therapy		
			EG 2 (32)	Passive movements with gentle joint compression (PMC)		
Zmyślna et al., 2019 (62)	CT	Patients aged 8–15 years old with a postural defect.	Control group CG (93)	Vojta therapy + PNF	The angle of thoracic kyphosis, lateral deviation of the spine, and spinal rotation (DIERS Formetric 4D system)	Statistically significant improvement in the body axis in all three planes was obtained in both groups. Neurophysiological rehabilitation of patients with postural defects produced positive effects by improving the angle of thoracic kyphosis, spinal rotation, and lateral deviation of the spine. Children with reduced thoracic kyphosis achieved less improvement in the kyphosis angle, lateral spinal deviation, and spinal rotation than children with kyphosis ≥42°.
			Vojta group EG (108)	Vojta therapy		

(Continued)

TABLE 5 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Michal et al., 2022 (68)	RCT	Children aged 10–12 years, diagnosed with idiopathic scoliosis with a low Cobb angle value.	Control group CG (15)	Corrective compensatory exercises antigravity, active and passive elongation, breathing, proprioception, and strengthening exercises.	Angle of trunk rotation (ATR) (scoliometer)	A significant reduction in the value of the ATR in the Vojta group. No significant changes in the value of the ATR were observed in CG.
			Vojta group EG (15)	Corrective compensatory exercises antigravity, active and passive elongation, breathing, proprioception, and strengthening exercises + Vojta therapy		
Ptak et al., 2022 (35)	CT	Healthy children have a slight delay in the phases of psychomotor development an average age of 7 months	Vojta Group 1 (11)	Children with increased muscle tone (IMT) Vojta therapy	The myotonometric measurement results consisted of the values of frequency, stiffness, elasticity, relaxation, and creep of the erector spinae. (The MYOTON device by Myoton AS Estonia) The normalization of the distribution of muscle tone was indirectly assessed (Munich Functional Developmental Diagnostic)	G1: changes in the viscoelastic parameters of the extensor muscles of the back occurred immediately after the therapy at the first examination. Whereas changes in the supporting and extensor function of the limbs occurred in both groups at the second examination.
			Vojta Group 2 (11)	Non-increased muscle tone (non-IMT). Vojta therapy		
Hohendahl et al., 2023 (63)	CT	Term birth infants with non-synostotic positional plagiocephaly therapy had to be initiated between 2 and 4 months of age.	Control group CG (91)	NDT according to the Bobath.	Cranial vault asymmetry index (CVAI) (standardized three-dimensional surface scans) and ear shift (calculated in millimeters).	The relative probability of success was 84% higher for Vojta compared to Bobath. Mean change of CVAI revealed a significantly greater reduction for infants treated with Vojta, as well as for ear shift. Improvement occurred especially from the age of 6–9 months. Treatment duration was significantly shorter with Vojta and severe cases of positional plagiocephaly benefited significantly more.
			Vojta group EG (98)	Vojta therapy		

(Continued)

TABLE 5 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Wójtowicz et al., 2017 (64)	RCT	Children aged 2–6 years with intellectual and motor disabilities	Control group CG (12)	Bobath, Ayres (sensory integration), Sherborne and Castillo Morales	Joint motion ranges, the Sagittal, Frontal Transverse Rotation (SFTR) measuring and recording system was used (international SFTR method of measuring and recording joint motion) The range of joint motion (in degrees by means of a goniometer). To evaluate manual skills (Gunzburg's PPAC Inventory as adapted by Witkowski).	Statistically significant results of comparing the first and second measurements for both methods, mostly in favor of the Vojta group. The Vojta method therapy is more effective than the other therapeutic methods in improving both upper limb motion and the self-service function of eating.
			Vojta group EG (12)	Vojta therapy		
Jung et al., 2017 (65)	RCT	Healthy infants aged 6–8 weeks with postural asymmetry	Control group CG (18)	Neurodevelopmental treatment handling and positioning + handling according to the Bobath concept	Restriction in head rotation and convexity of the spine in prone and supine positions before and after therapy (standardized and blinded video-based asymmetry scale developed by Philippi et al.)	While both Neurodevelopmental treatment and Vojta are effective in the treatment of infantile postural asymmetry, therapeutic effectiveness is significantly greater within the Vojta
			Vojta group EG (19)	Vojta therapy		
Bragelien et al., 2007 (66)	RCT	Premature infants on NG feeds <36 weeks and not on assisted ventilation	Control group (18)	Standard nursing care without intervention.	Weaning from NG feeding post-menstrual age at discharge.	The stimulation program did not result in earlier weaning from NG feeding or earlier discharge in both groups.
			Vojta group (18)	Vojta therapy		

RCT, randomized controlled trial; CT, clinical trial; EG, experimental group; CG, control group; VT, Vojta therapy; PMC, passive movements with gentle joint compression; PMC, passive movements with gentle joint compression; NIPS, Neonatal Infant Pain Scale; PNF, proprioceptive neuromuscular facilitation; ATR, angle of trunk rotation; IMT, increased muscle tone; NDT, neurodevelopmental treatment; CVAI, cranial vault asymmetry index; SFTR, sagittal, frontal transverse rotation; NG, nasogastric.

"excellent" in one of them. The most frequent biases were related to therapist blinding. In the reliability analysis, the agreement between the two reviewers regarding the methodological quality of the included studies was excellent, according to the kappa coefficient ($k = 0.90$).

3.8 Effects of VT in adults

3.8.1 Effects of VT on neurophysiological functions

Evaluation of the effectiveness of VT on muscle activity and cortical activation was performed. The effects of VT on muscle activity were significant when compared with the control group (SMD = 0.81; 95% CI: 0.41–1.21; $n = 770$; $Z = 3.98$; $p < 0.001$) with substantial heterogeneity ($I^2 = 82\%$; $p < 0.001$) (Figure 3). The sensitivity analysis was performed by eliminating from the analysis the studies by Perales López et al. (common finger extensor 2), Sánchez Gonzáles et al. (left external oblique), and Sanz et al. (right forearm 3), which were outliers. Sensitivity analysis maintained significance in favor of the VT group, reducing effect size and heterogeneity (SMD = 0.48; 95% CI: 0.27–0.69; $n = 624$; $Z = 4.54$; $p < 0.001$, $I^2 = 25\%$; $p = 0.17$).

The effects of VT on cortical activation were significant when compared with the control group (SMD = 0.25; 95% CI: 0.1–0.41; $n = 774$; $Z = 3.22$; $p = 0.001$) with low heterogeneity ($I^2 = 14\%$;

TABLE 6 Characteristics of the included studies on pediatrics with respiratory disorders.

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Bhöme et al., 1995	CT	Premature infants	Vojta group (11)	Vojta therapy	Air flow (pneumotachometer) Esophageal pressure (pressure sensor)	Decreases work of breathing in relation to ventilated volume and improves compliance. Improves pulmonary mechanics and reduces work of breathing, maintaining unchanged airway resistance and minute volume.
Ha et al., 2018 (52)	RCT	Children with spastic cerebral palsy	CG (5)	Trunk strengthening exercises and gait training.	Gross motor function (GMFM-88) Diaphragmatic movements in inspiration and expiration (ultrasound)	Significant difference between before and after GMFM-88 for sitting and in the improvement changes for inspiration in the Vojta group but not in the CG. For changes in diaphragmatic area for expiration there were no significant changes in both groups.
			Vojta Group EG (5)	Vojta therapy		
Giannantonio et al., 2010 (69)	CT	Premature newborns	Vojta Group 1 (21) hyaline membrane disease, under treatment with nasal CPAP	Vojta therapy	Respiratory rate, $SatO_2$, transcutaneous $PtcCO_2$ e $PtcO_2$ To evaluate the onset of stress or pain following the stimulations (NIPS score and the PIPP score) Risk of brain damage (cerebral ultrasound scans and color Doppler unit.)	Caused an increase in $PtcO_2$ and $SatO_2$ values. No negative effects on $PtcCO_2$ and respiratory rate. Were observed, NIPS and PIPP stress scores remained unmodified during the treatment. In no patient, the images of the CNS worsened over time and none of the infants developed periventricular leukomalacia.
			Vojta Group 2: (13) persistent pneumonia under treatment with oxygen therapy.			

(Continued)

TABLE 6 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Gharu et al., 2016 (70)	RCT	Preterm Infants	Control group CG (30)	Respiratory physiotherapy	Oxygen saturation (pulse oximeter)	In the short term, both groups improve SPO_2 equally. In the long term, the Vojta group improves more significantly than the CG, with improvements observed in both groups.
			Vojta group EG (20)	Vojta therapy		
Kole et al., 2014 (71)	RCT	Premature infants	CG1 (20)	Conventional respiratory physiotherapy (CPT)	SpO_2 (Pulse oximetry) PaO_2 (Arterial blood gas values) SaO_2 (Arterial oxyhemoglobin saturation). Re-expansion pulmonaire (Chest X-ray)	These are safe and effective methods to improve oxygenation and reduce atelectasis. Improved SPO_2 and PaO_2 on the first and last day in all groups significantly without significance in group comparison. Chest X-ray demonstrated re-expansion of collapsed airways.
			CG2 (20)	Pulmonary compression technique + CPT		
			Vojta group (20)	CPT + Vojta therapy		
Kaundal et al., 2016 (72)	RCT	Premature infants	Control group CG (30)	Chest physiotherapy	Oxygen saturation ($SatO_2$%) Respiratory rate	Both CG and EG increase saturation of peripheral oxygen and decrease in respiratory rate. Chest physiotherapy along with VT is found better than chest physiotherapy alone in improving oxygen saturation and respiratory rate in preterm infants with SDR.
			Vojta group EG (30)	Vojta therapy + Chest physiotherapy		

(Continued)

TABLE 6 (Continued)

Study	Design	Population	Group (sample size)	Protocol intervention	Outcomes	Results
Maha et al., 2023 (74)	CT	Preterm neonates	Control group (19)	Conventional chest physiotherapy (CPT) in the form of chest percussion, modified postural drainage, and vibration techniques.	Respiratory Rate, SaO_2 (pulse oximeter) O_2 days Days in NICU	Statistically significant increase in the mean values of $SatO_2$ and a decrease in the mean value of RR measured at discharge in both groups. Statistical significant decrease in the mean value of oxygen days in group Vojta when compared with its corresponding value in CG. Statistical significant decrease in the mean value of days in NICU in Vojta group.
			Vojta group EG (18)	Vojta therapy		
Ha et al., 2016 (47)	RCT	Young healthy adults	Control group CG (7)	Arbitrary point.	The thickness of the muscles (EO), the (IO), the (TrA) and (RA) (ultrasonic image) the area of the diaphragm during inspiration and expiration (ultrasonograph) Maintaining a consistent level of stimulation (Algometer)	Vojta group: the thickness of the TrA and the diaphragm significantly increased during stimulation while the thickness of the EO significantly decreased in normal adults. Considerable change in the area of the diaphragm during inspiration and expiration in the Vojta group, but not in the CG.
			Vojta group EG (7)	Vojta therapy		

RCT, randomized controlled trial; CT, clinical trial; EG, experimental group; CG, control group; VT, Vojta therapy; RDS, respiratory distress syndrome; GMFM-88, gross motor function measurement-88; CPAP, continuous positive airway pressure; NIPS, neonatal infant pain score; PIPP, perinatal infant pain profile; $SatO_2$, oxygen saturation; $PtcCO_2$, transcutaneous carbon dioxide pressure; $PtcO_2$, transcutaneous oxygen pressure; PaO_2, arterial blood gas pressure; RR, respiratory rate; NICU, neonatal intensive care unit; CNS, central nervous system; CPT, conventional chest physiotherapy; EO, external oblique abdominal; IO, internal oblique abdominal; TrA, transversus abdominis; RA, rectus abdominis.

$p = 0.28$) (Figure 4). Subgroup analysis showed that there were non-significant differences in different balance assessments ($p = 0.48$), but a significant difference was observed in favor of VT in left premotor cortex (SMD = 0.48; 95% CI: 0.12–0.85; $n = 120$; $Z = 2.6$; $p = 0.009$), left SMA (SMD = 0.43; 95% CI: 0.07–0.79; $n = 120$; $Z = 2.34$; $p = 0.02$), and right SMA (SMD = 0.39; 95% CI: 0.03–0.75; $n = 120$; $Z = 2.13$; $p = 0.03$). Sensitivity analysis could not be performed since the overall analysis was performed in three studies.

3.8.2 Effects of VT clinical trials in adults with neurological diseases

Evaluation of the effectiveness of VT on balance in people with MS was performed. The effects of VT were significant when compared

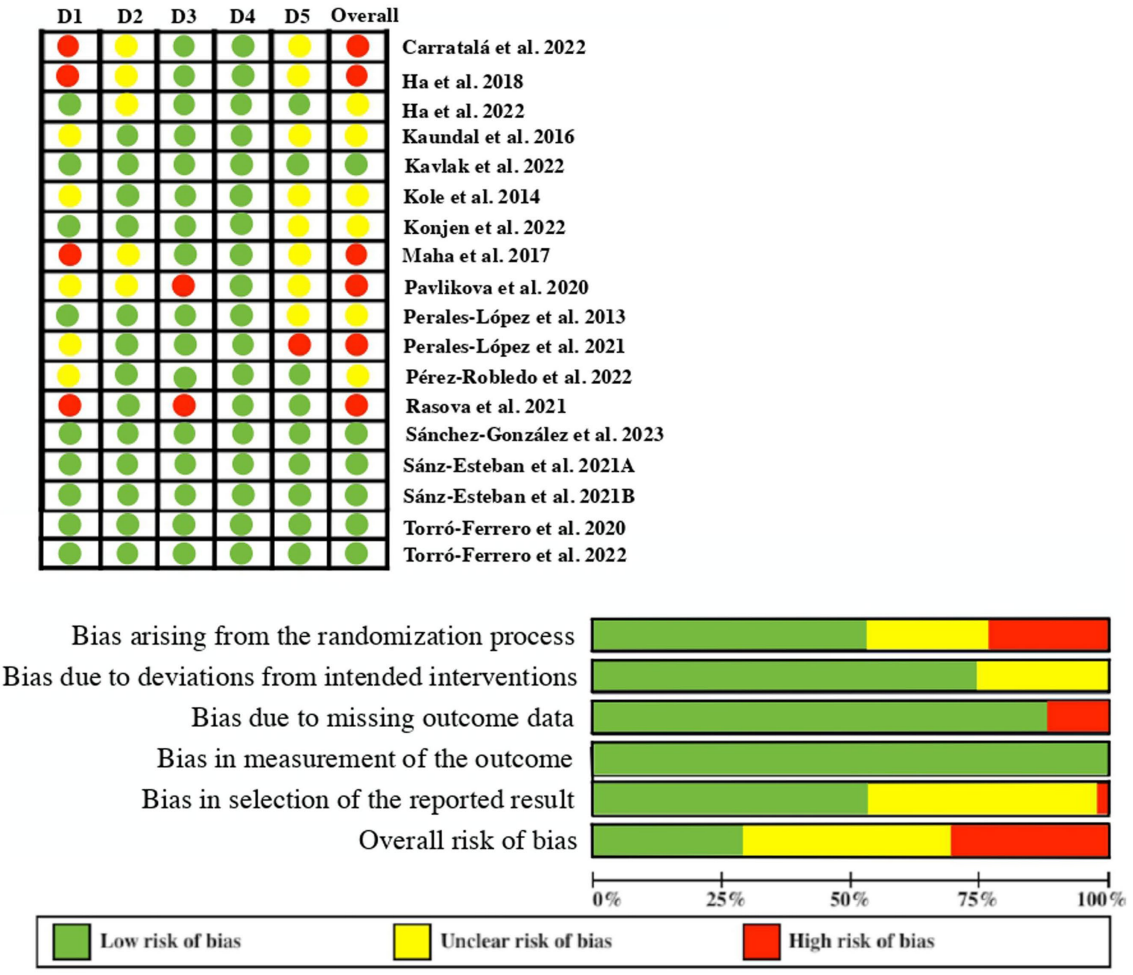

FIGURE 2
Assessment of the risk of bias according to the revised Cochrane risk-of-bias tool for randomized trials (ROB-2).

with the control group (SMD = 0.5; 95% CI: 0.17–0.83; $n = 315$; $Z = 2.96$; $p = 0.003$) with moderate heterogeneity ($I^2 = 47\%$; $p = 0.07$) (Figure 5). Subgroup analysis showed that there were non-significant differences in different balance assessments ($p = 0.09$), but a significant difference was observed in favor of VT in the tandem test (SMD = 1.1; 95% CI: 0.51–1.69; $n = 60$; $Z = 3.64$; $p < 0.001$). Sensitivity analysis could not be performed since the overall analysis was performed in three studies.

3.9 Effects of VT in pediatrics

3.9.1 Effects of VT in children and premature babies with respiratory disorders

Evaluation of the effectiveness of VT on oxygen saturation levels and respiratory rate was performed. The effects of VT on oxygen saturation levels were non-significant when compared with the control group (SMD = 0.11; 95% CI: −0.33 to 0.56; $n = 171$; $Z = 0.5$; $p = 0.62$) with moderate to substantial heterogeneity ($I^2 = 52\%$; $p = 0.08$) (Figure 6). Subgroup analysis showed that there were non-significant differences between Sp02, PaO_2, and SO_2 ($p = 0.68$). Sensitivity analysis could not be performed since the overall analysis was performed in three studies.

The effects of VT on respiratory rate were non-significant when compared with the control group (SMD = 0.7; 95% CI: −0.31 to 1.71; $n = 93$; $Z = 1.35$; $p = 0.18$) with substantial heterogeneity ($I^2 = 82\%$; $p = 0.02$) (Figure 7).

3.9.2 Effects of VT in pediatric patients with non-neurological disorders

Evaluation of the effectiveness of VT on weight, height, and head circumference was performed. The effects of VT on orthopedic disorders were non-significant when compared with the control group (SMD = −0.01; 95% CI: −0.47 to 0.45; $n = 318$; $Z = 0.04$; $p = 0.97$) with substantial heterogeneity ($I^2 = 75\%$; $p = 0.001$) (Figure 8). Subgroup analysis showed that there were non-significant differences between weight, height, and head circumference ($p = 0.68$), but a significant difference was observed in favor of the control group in weight gain (SMD = −0.7; 95% CI: −1.09 to −0.3; $n = 106$; $Z = 3.48$; $p < 0.001$). Sensitivity analysis could not be performed since the overall analysis was performed in three studies.

10.3389/fneur.2024.1391448

TABLE 7 Methodological score of randomized clinical trials using the Physiotherapy Evidence Database (PEDro) scale.

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Studies on neurological evidence												
Pérez-Robledo et al., 2022 (24)	Y	N	N	Y	N	N	Y	Y	Y	Y	Y	6
Sanz-Esteban et al., 2021 (26)	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	7
Sanz-Esteban et al., 2021 (27)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Sanz-Esteban et al., 2018 (28)	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	7
Hok et al., 2019 (29)	N	Y	Y	Y	Y	N	Y	N	N	Y	Y	7
Hok et al., 2017 (30)	N	Y	Y	Y	Y	N	Y	N	N	Y	Y	7
Opavsky et al., 2018 (32)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	9
Sánchez-González et al., 2023 (33)	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8
Řasová et al., 2021 (40)	Y	Y	Y	N	N	N	Y	N	N	Y	Y	5
Prochazkova et al., 2021 (34)	Y	Y	Y	N	N	N	Y	Y	N	Y	N	5
Perales-López et al., 2013 (37)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Studies on clinical evidence in adults with neurological disorders												
M Pavlikova et al., 2020 (42)	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	7
G Angelova et al., 2020 (41)	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Lopez et al., 2021 (46)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Carratalá-Tejada et al., 2022 (45)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	6
Epple et al., 2020 (43)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
Řasová et al., 2021 (40)	Y	Y	Y	N	N	N	Y	N	N	Y	Y	5
Studies on clinical evidence in adults with orthopedic disorders												
Ha et al., 2016 (47)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Juárez et al., 2021 (48)	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Studies on clinical evidence in pediatric neurological disorders												
Ha et al., 2018 (52)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Ha et al., 2022 (53)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Kavlak et al., 2022 (54)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Nipaporn et al., 2022 (59)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Sung et al., 2019 (58)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Studies on clinical evidence in pediatrics with non-neurological disorders												
Torró-Ferrero et al., 2022 (67)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9
Torró-Ferrero et al., 2022 (61)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10

(Continued)

TABLE 7 (Continued)

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Michal et al., 2022 (68)	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	7
Wójtowicz et al., 2017 (64)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Jung et al., 2017 (65)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Bragelien et al., 2007 (66)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Studies on clinical evidence in pediatric respiratory disorders												
Ha et al., 2018 (52)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Gharu et al., 2016 (70)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Kole et al., 2014 (71)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Kaundal et al., 2016 (72)	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	8
Ha et al., 2016 (47)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6

Y, yes; N, no. 1: eligibility criteria specify; 2: random allocation of participants; 3: concealed allocation; 4: similarity between groups at baseline; 5: participant blinding; 6: therapist blinding; 7: assessor blinding; 8: dropout rate less than 15%; 9: intention-to-treat analysis; 10: between-group statistical comparisons; 11: point measures and variability data.

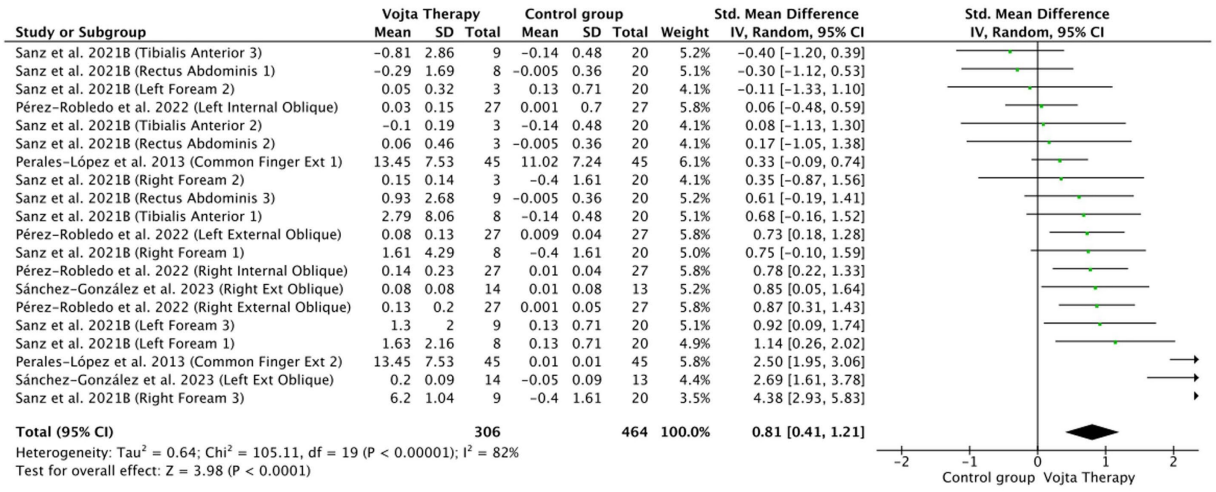

FIGURE 3
Effects of Vojta Therapy compared to control on adult muscle activity. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI). The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond represents the overall mean difference of the studies.

3.9.3 Effects of VT in pediatric patients with neurological disorders

Evaluation of the effectiveness of VT on gross motor function was performed. The effects of VT on gross motor function were non-significant when compared with the control group (SMD = −0.02; 95% CI: −0.32 to 0.27; $n = 179$; $Z = 0.16$; $p = 0.87$) with low heterogeneity ($I^2 = 0\%$; $p = 0.49$) (Figure 9). Subgroup analysis showed that there were non-significant differences between the different scores of the gross motor function test and the Alberta scale ($p = 0.95$). Sensitivity analysis could not be performed since the overall analysis was performed in three studies.

3.10 Quality of evidence

Table 8 provides the details of the GRADE assessment. In the assessment of the quality of evidence, according to the GRADE scale, the overall quality of the evidence is classified as "very small." The small number of studies, the risk of bias in some studies, the heterogeneity among the included studies, and the small effect size of the results have reduced the level of evidence for the overall effect.

4 Discussion

In summary, this systematic review with meta-analysis found significant differences in cortical activity and muscle activity in adults undergoing VT compared to the control group. Significantly better results in improving balance in people living with multiple sclerosis (MS) when using VT have also been confirmed when compared with other techniques such as balance, core, or trunk control exercises. Non-significant differences were found when evaluating outcomes such as gross motor function, oxygen saturation, respiratory rate,

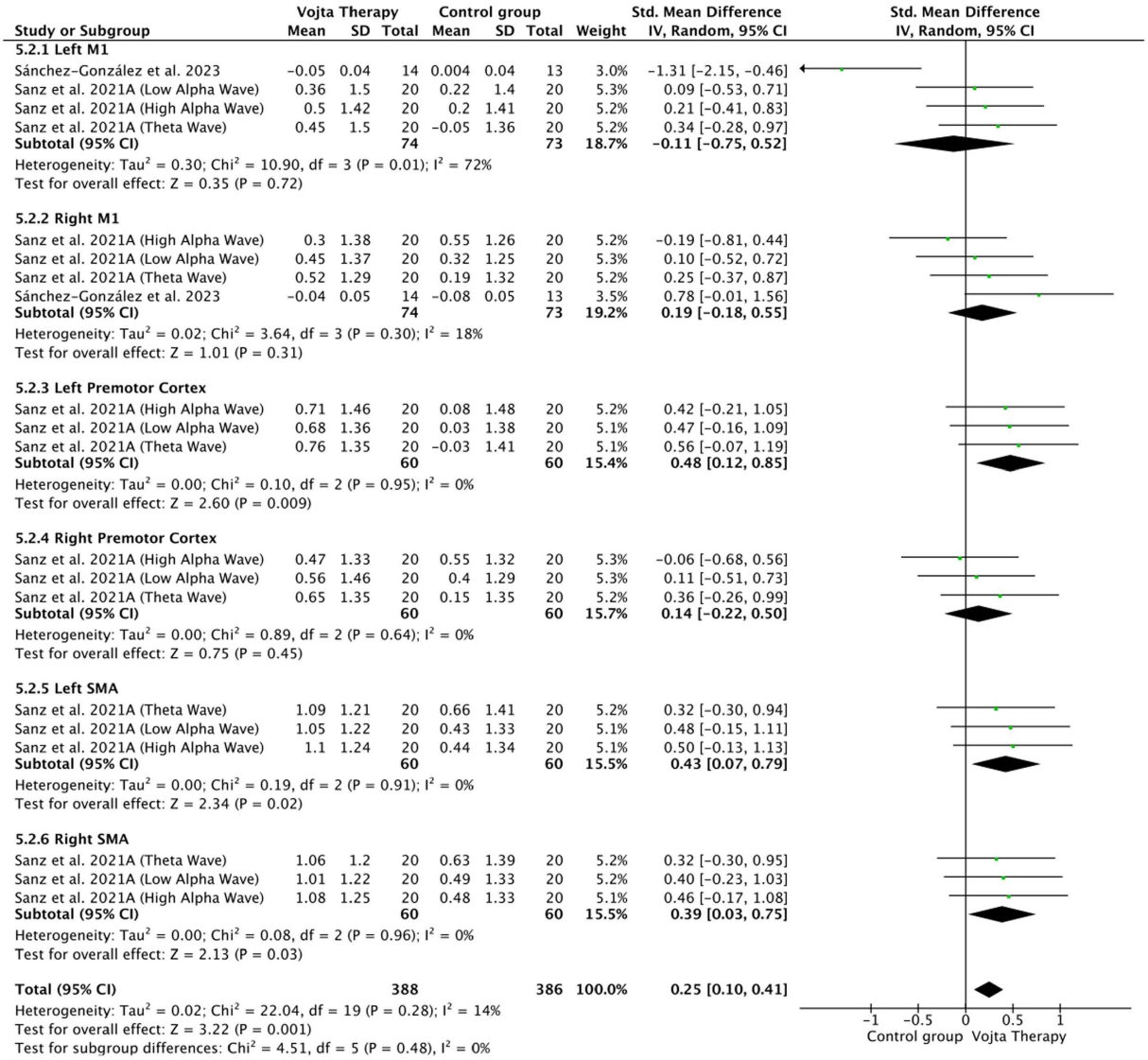

FIGURE 4
Effects of Vojta Therapy compared to control on adult cortical activation. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI). The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond represents the overall mean difference of the studies.

height, and head circumference in pediatric respiratory, neurological, and non-neurological conditions. Non-significant differences between groups in other conditions suggest that VT is as efficient as other approaches in improving patients with neurological, orthopedic, and respiratory conditions.

The quality of the RTC showing positive effects using VT was "good or excellent" in all the conditions studied. In them, VT was plotted against a large variety of interventions aiming to address distinct domains (2) of the same underlying condition. The VT principle neuromodulates the common dysfunction in the conditions described: the automatic adjustments of posture and movement functions. The control groups included standard kinesitherapy exercises, TENS, cryotherapy, NDT-like, FES, proprioceptive and other sensory-motor approaches, balance exercises, core exercises, treadmill walk training, stretching, strengthening, goal/task-directed training, lung squeeze techniques, conventional or chest physiotherapy, manual therapy, and massage therapy. This exemplifies the number of therapies to which patients are frequently subjected and, therefore, the difficulty of understanding the individual effect among therapies or compared to the natural history of a specific disease. This is especially relevant in studies of higher quality from a methodological point of view, such as RTC, making their generation difficult for ethical reasons (randomization or comparison against placebo), as well as the infrastructure required in clinical services focusing on maximizing their care capacity. As a result, there is a current debate about recognizing the value of studies with a pre-post design in this field (75), allowing participants to perform as their own controls. Although not included in the meta-analysis, our study collected seven pre-post design CT isolating VT interventions, and their

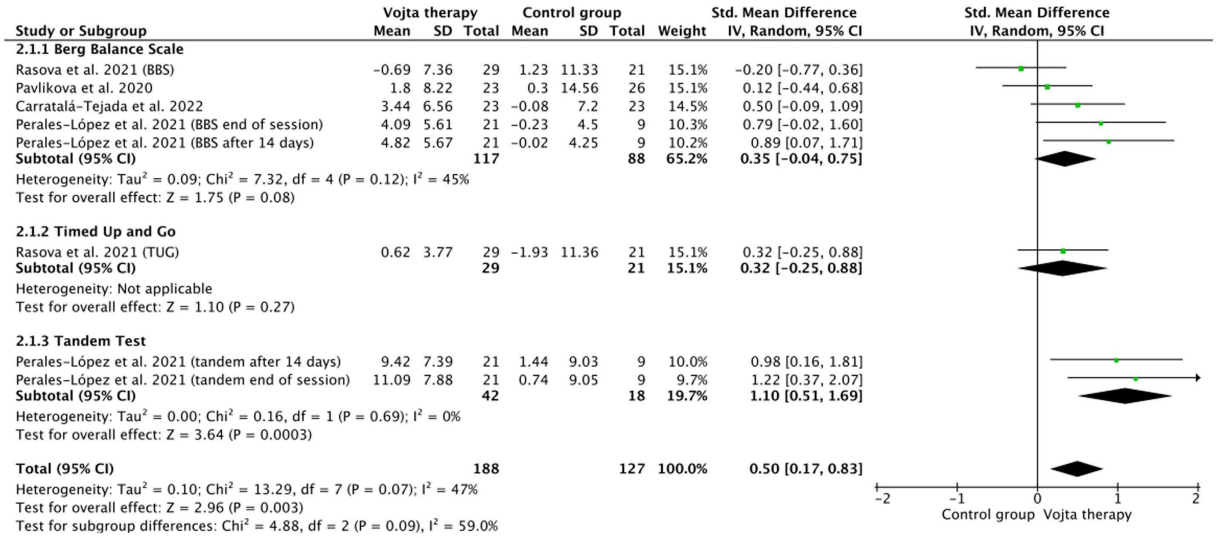

FIGURE 5
Effects of Vojta Therapy compared to control on balance in people living with multiple sclerosis. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI). The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond represents the overall mean difference of the studies.

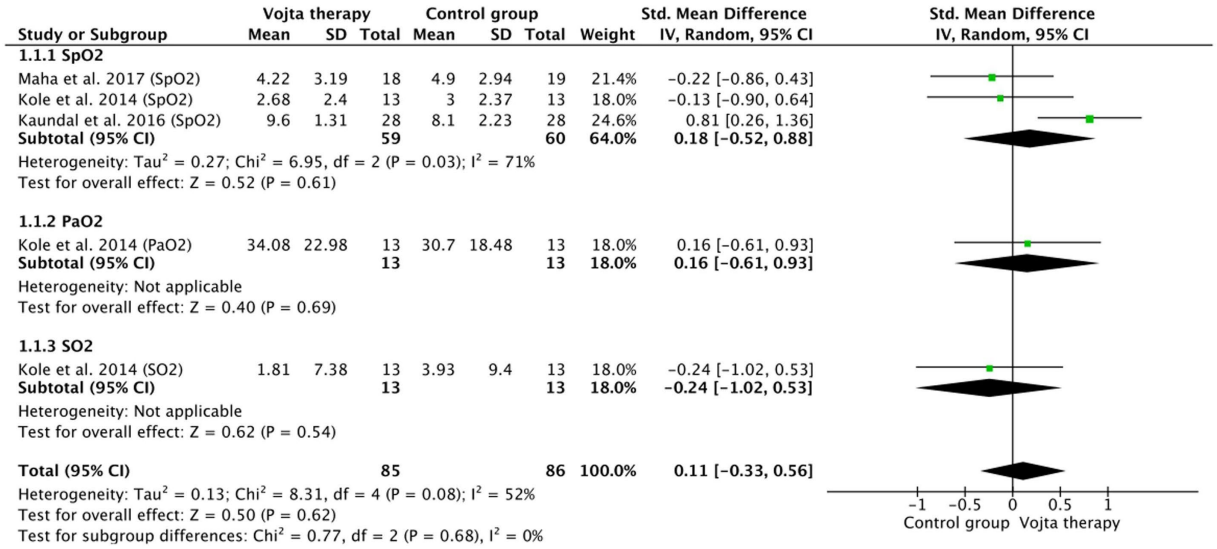

FIGURE 6
Effects of Vojta Therapy compared to control on oxygen saturation levels in children and premature babies. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI). The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond represents the overall mean difference of the studies.

conclusions portray: (a) significant improvements in acceleration acquisition of gross motor function items in children with CP (56); (b) timed gait test and gait parameters in children with CP (57) and stroke (44); (c) improvements in pain and gait parameters in adults with low back pain (49, 50); (d) improvements in SO_2, PaO_2, and $PtcO_2$ without altering $PtcCO_2$ in premature children (69, 71) while decreasing respiratory rate (72) as well as improvements in compliance and dysphagia and reduction of work of breathing in relation to ventilated volume (73).

4.1 Neurophysiological evidence: motor control and motor behavior

This systematic review is the first work integrating two complementary concepts in the field, commonly contributing to misunderstandings due to partial perspectives: improvements in functional outcomes easily accessible in clinical practice (motor behavior), with underlying neurophysiological mechanisms supporting these changes (motor control). VT improved motor

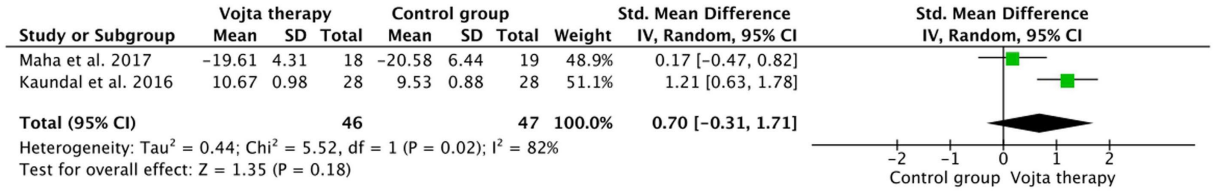

FIGURE 7
Effects of Vojta Therapy compared to control on respiratory rate in children and premature babies. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI). The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond represents the overall mean difference of the studies.

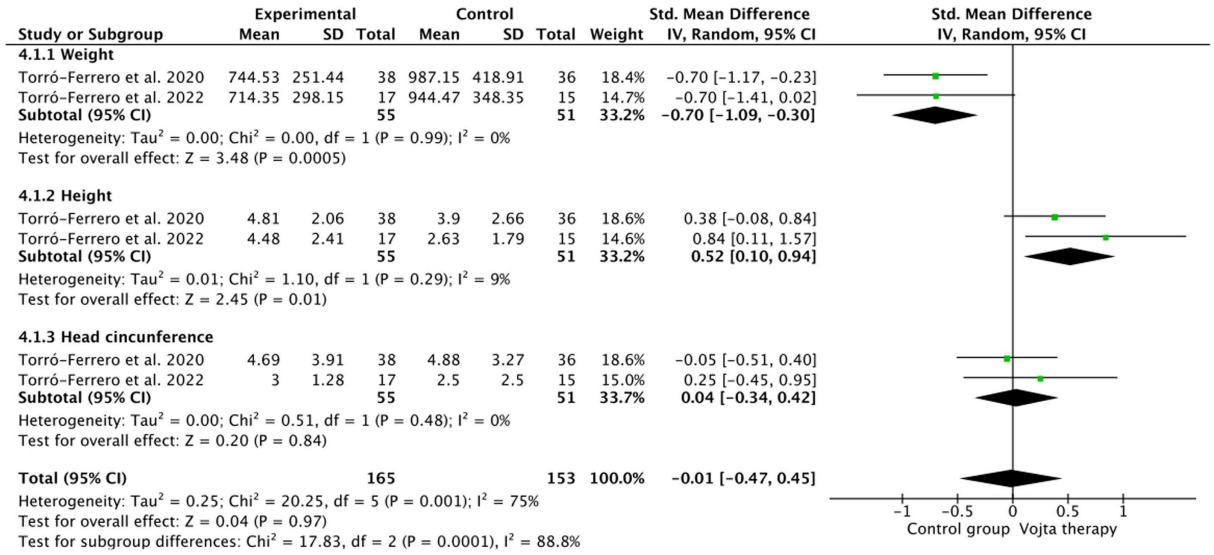

FIGURE 8
Effects of Vojta Therapy compared to control on weight, height, and head circumference in children and premature babies. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI). The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond represents the overall mean difference of the studies.

behavior, as measured by gross motor performance, muscle thickness and tone, pain, ROM, postural alignment, walking and functionality tests, gait parameters, respiratory-gasometrical measurements, bone mineralization, bone formation, and anthropometrics. In addition, these findings were supported by significant changes in the mechanisms underlying motor control. Neurophysiological changes after VT application on muscle activity, as well as cortical (specifically motor cortex) activation, were significant when compared with the control group (24, 30, 33, 34). The equivalent results observed in other therapies will require individual investigation to understand if changes are plasticity-related and limited to the transmission of signals to muscles resulting in improved motoneuronal recruitment and rate coding as well as muscle fiber hypertrophy (motor behavior) rather than to changes in motor control (1) processes as expected in neurophysiotherapy techniques.

The neural circuits established between the thalamus, basal ganglia, and cortex, together with the action of the cerebellum, are necessary to ensure correct motor control, including learning and adaptation (76).

The supplementary motor area (SMA) plays an important role in the preparation, initiation, and execution of movements (77). Authors, including Takakusaki et al. (78), described a direct interconnection among the primary motor area (M1), SMA, and premotor area, along with the basal ganglia and the cerebellum.

Numerous current therapies have shown significant improvements in adults with neurological disorders (robot-assisted training, virtual reality, functional electrostimulation, brain stimulation, and neuromodulation) (21). The foundation of these interventions lies in the plastic changes that can be induced in the supplementary, premotor, and motor areas associated with movement. Other recommended methodologies for pediatric patients with cerebral palsy (gait training, physical activity, and intensive therapy) are based on sensory inputs and motor learning (79), eliciting neuroplastic modifications in the previously described areas (21).

The neurophysiological effects produced in cortical and subcortical structures point to the activation of thalamo-cortical circuits, basal ganglia, and supplementary motor area involved in motor control and movement learning (28). VT is in close alignment with contemporary neuroscience concepts, substantiated by clinical evidence and supported by studies, positioning it as a neurorehabilitation tool consistent with the plasticity, motor control, and learning objectives proposed by other therapeutic techniques.

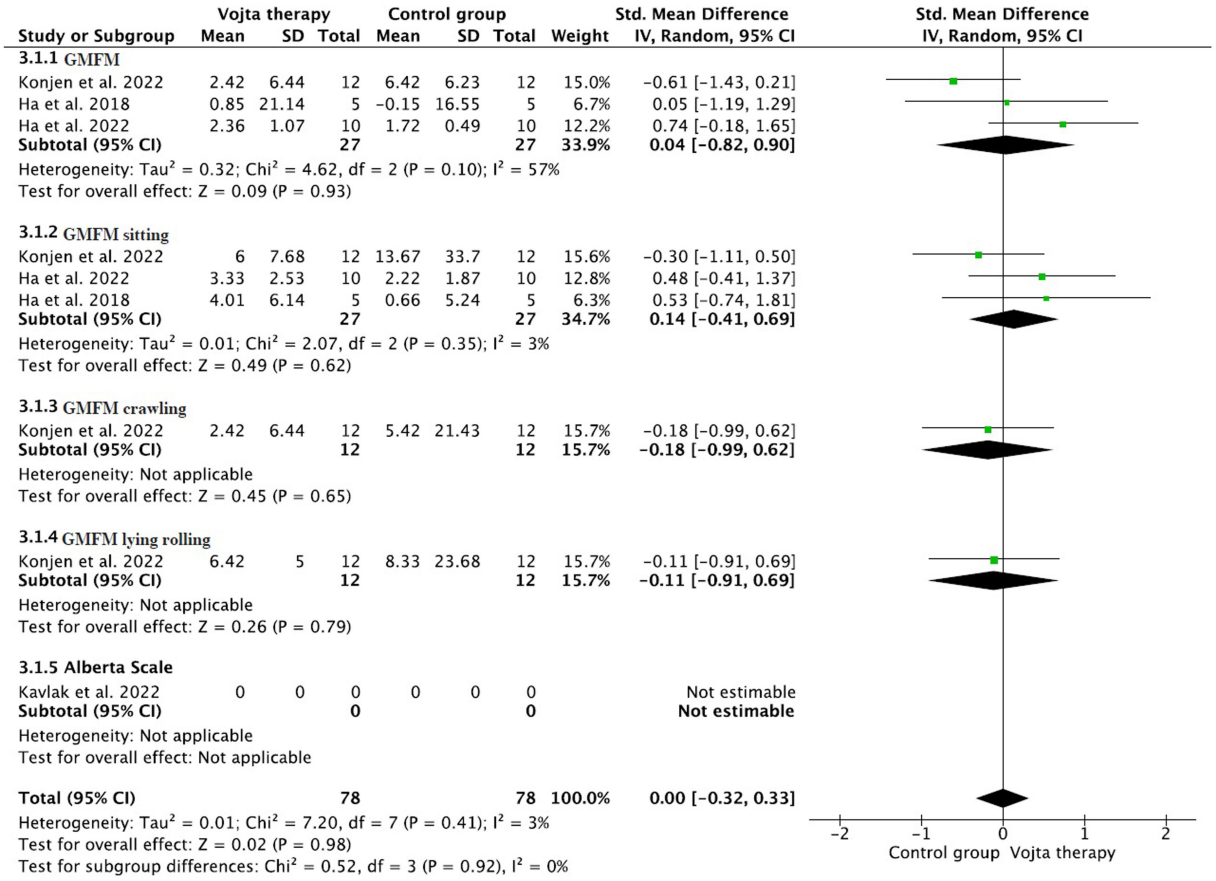

FIGURE 9
Effects of Vojta Therapy compared to control on gross motor function in pediatric patients with neurological disorders. Forest plot of the results of a random-effects meta-analysis shown as standardized mean differences (SMD) with 95% confidence interval (CI). The shaded square represents the point estimate for each individual study and the study weight in the meta-analysis. The diamond represents the overall mean difference of the studies. GMFM = Gross Motor Function Measure.

4.2 Neurophysiotherapy translational research

Researchers have a valid need for data (80), but conducting experiments based on principles that have yielded negative results in previous studies due to methodological shortcomings is not advised. This vicious cycle can only be broken with cooperation instead of confrontation, considering that evidence-based practice integrates individual clinical expertise with the best available external clinical evidence from systematic research (81). Currently, external evidence successfully demonstrates the efficacy of VT in enhancing balance among individuals with MS. However, this superiority is not observed when VT is compared with other techniques in diverse patient populations. In these cases, when the diverse quantification of motor behavior and occupational parameters does not allow a deeper meta-analysis, a relevant role is acquired by the knowledge obtained through theoretical reasoning from the basic sciences to guide clinical practice (81). The VT principle neuromodulates the common dysfunction in the conditions described: the automatic adjustments of posture and movement functions. A specific pre-post CT design could isolate the elicitation of gross motor function through VT neuromodulation of postural function without functional training. This central regulation of automatic ontogenetic postural function, improving motor control, has also been supported by direct CNS changes and the diverse positive results in the same population [premature respiratory function, bone formation (61), bone mineralization (67), and suction (82)]. Other criteria for therapeutic (Sorry missing T on my corrections) selection would be the good results shown by VT in stress-related parameters (25, 61, 67, 69), while evidence is unclear in other respiratory techniques.

While survival rates of preterm infants have improved, long-term morbidity remains a significant concern: respiratory distress syndrome, bronchopulmonary dysplasia, CNS lesions, suction and swallowing disorders, osteopenia of prematurity, cardiac problems, and a greater likelihood of experiencing stress and pain during medical procedures. VT is postulated as the gold standard treatment for preterm infants, offering a single non-invasive intervention to improve each and every one of these health challenges (6).

4.3 Children and premature babies with respiratory disorders

One of the main long-term sequelae of preterm birth remains respiratory distress syndrome, which is mainly contributed by the effect of early lung inflammation superimposed on immature lungs (83).

TABLE 8 GRADE evidence for Vojta therapy.

Number of studies	Risk of bias	Inconsistency†	Indirectness‡	Imprecision§	Publication bias	SMD (95% CI)	Quality of evidence
Effects of tDCS on adults							
Effects of VT on neurophysiological tests							
Muscle activity							
Four trials ($n = 211$)		Very serious ($I^2 = 82\%$)	No serious	No serious	No serious	0.18 (0.41, 1.21)	Very small
Cortical activity							
Two trials ($n = 67$)		No serious ($I^2 = 14\%$)	No serious	No serious	No serious	0.25 (0.1, 0.41)	Very small
Effects of VT clinical trials in adults with neurological diseases							
Balance							
Four trials ($n = 172$)	No serious	Serious ($I^2 = 47\%$)	No serious	No serious	No serious	0.5 (0.17, 0.83)	Very Small
Effects of tDCS on pediatrics							
Effects of VT in children with respiratory disorders							
SpO_2							
Three trials ($n = 119$)	Serious	Serious ($I^2 = 52\%$)	No serious	No serious	No serious	0.11 (−0.33, 0.56)	Very small
Respiratory rate							
Two trials ($n = 93$)	Serious	Very serious ($I^2 = 82\%$)	No serious	No serious	No serious	0.70 (−0.31, 1.71)	Very small
Effects of VT in pediatric patients with non-neurological disorders							
Orthopedic disorders							
Two trials ($n = 106$)	No serious	Very serious ($I^2 = 75\%$)	No serious	No serious	No serious	−0.01 (−0.47, 0.45)	Very small
Effects of VT in pediatric patients with neurological disorders							
Gross motor function							
Four trials ($n = 77$)	Serious	No serious ($I^2 = 0\%$)	No serious	No serious	No serious	−0.02 (−0.32, 0.27)	Very small

GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; SMD, standardized mean difference. * "No" = most information is from results at low risk of bias; "Serious" = crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect; "Very serious" = crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect. † "Serious" = $I^2 > 40\%$; "Very serious" = $I^2 > 80\%$. ‡ No indirectness of evidence was found in any study. § Based on sample size. "Serious" = $n < 250$ subjects; "Very serious" = $n < 250$ and the estimated effect is little or absent. ¶Based on funnel plots. No publication bias was found. Funnel plots are not shown because the number of trials was less than 10.

Conventional neonatal respiratory therapy techniques focus on secretion clearance (84). The mechanism of action by which VT works is unique compared to other respiratory physiotherapy treatments. VT onset posture and movement patterns originated in the CNS, improving ventilatory function by restoring adequate breathing synergies. This is even more relevant in restrictive disorders with deficits in active insufflation capacities. Changes in respiratory muscle thickness may be attributed to this induction of motor and postural muscle synergies, suggesting that VT actively works to modify active inspiratory functional capacity, leading to changes that are maintained over time. Changes in diaphragm thickness, as well as in diaphragmatic area and increased excursion during inspiration, have been related to improvements in respiratory function (47, 52), and re-expansion of collapsed airways; this was not the case in the control group (71). It has also been related to changes in the thickness of the transversus abdominis muscle (47) and other abdominal muscles (24, 52, 53) that play a role in improving ventilatory function. These changes in active inspiratory capacity in premature infants caused by VT are maintained over time, unlike other respiratory physiotherapy

interventions (70). Although there are general benefits in respiratory function with the application of all techniques, in studies that make comparisons between groups, there is a statistically significant decrease in the mean value of oxygen days, and the results also revealed a statistically significant decrease in the mean value of days in the NICU in the VT group when compared with its corresponding value in the control group (74), respiratory rate, and SpO_2 (72).

Sucking and swallowing are some of the most complex abilities that premature newborns face due to their anatomofunctional immaturity and improper sensoriomotor integration due to the high energy requirements that require breathing coordination (85). TV has shown positive effects on this very important function, which, if altered, keeps premature babies hospitalized for longer. TV would, unlike other interventions, seem to have a direct impact on the central pattern generator, which improves the rhythmicity as well as the regularity of both non-nutritive and nutritive sucking in premature newborns (82). On the other hand, the stimulation program would seem to have no effect on earlier weaning from nasogastric feeding (66).

Preterm infants exhibit lower levels of mineralization, a condition known as osteopenia of prematurity, which is marked by a reduction in bone mineral content; it is multifactorial, progressive, and variable in severity (86). A situation that leads, in the long term, to a reduction in maximum bone mass, weaker bones, shorter stature, and an increased risk of fracture compared with those born at term (87). We may conclude that VT is an effective treatment for increasing bone formation and growth in preterm infants. This fact may have a positive effect on the prevention and treatment of osteopenia from prematurity. Furthermore, VT has been shown to be more effective than other physical therapy modalities (61, 67).

Premature birth severely disrupts normal organ system development, leading to long-lasting adverse effects such as high blood pressure and cardiac dysfunction (88). Very preterm infants are at high risk of developing hemodynamically significant patent ductus arteriosus and are associated with a high risk of intraventricular hemorrhage (IVH) and/or massive pulmonary hemorrhage (89). VT could also be considered safe for protecting the heart since in young adults it has been measured that the heart rate and respiration rate decreased after active stimulations, and this usually occurs in a relaxed condition (32).

Immature infants often require intensive care treatment involving many painful or stressful diagnostic and therapeutic procedures, as well as uncomfortable interventions (90). As survival rates in the NICU improve, focus increases on reducing neurological issues in premature infants. Studies show a link between frequent painful procedures and decreased head growth and impaired brain function in these infants (91). It is imperative to reduce the number of interventions and procedures in the NICU, and this is why VT is again recommended as the intervention of choice for physical therapy. A single short-term intervention that has not only demonstrated improvements in ventilatory function, suction-swallowing, prevention of osteopenia of prematurity, and treatment and prevention of cerebral motor alterations, but it is also a safe technique. It does not cause stress or pain in measurements with the NIPS and PIPP scales in exactly this population (61, 69), and in no patient, the images of the CNS worsened over time, and none of the preterm patients developed periventricular leukomalacia (69). In the same way, it was verified that there was no increase in the concentration of cortisol in saliva detected in infants with central coordination disorders directly after VT (25).

In agreement with previous authors and considering the above, VT is recommended as an intervention technique for premature children.

4.4 Pediatric patients with non-neurological disorders

Physical therapists have access to various international methods for treating scoliosis. Among the interventions endorsed by the International Society on Scoliosis Orthopedic and Rehabilitation Treatment is the stabilization of corrected posture. Schroth, one of the most recommended methods, emphasizes VT approach (92) and recommends that for patients under 10 years of age or those lacking the necessary cognitive capacity and active collaboration, alternative solutions should be sought to address spinal deviations, suggesting the use of VT, probably because of its effects on postural control through reflex activation of the CNS. We can check through the findings of two CT and one RCT, indicating that VT has a positive impact on managing three-dimensional deviations of the spine, such as scoliosis, as well as deviations in an isolated plane. These observations have been documented in populations of both children and adolescents (62, 68), as well as in infants under 1 year of age with postural asymmetry (65). Similarly, we derive benefits from the application of VT in other types of asymmetries in infants, such as limitations in head and trunk rotation (65) or significant improvements in reducing plagiocephaly, with shorter intervention times and reduced asymmetry in head rotation and postural trunk alterations compared to other interventions (63).

4.5 Equality in the evidence-based field

Physiotherapy advocates the importance of removing barriers for our patients to manifest their best potential. This principle is equally applicable to evidence-based practices within the health profession. Our SR also reflects the large effort of clinical physiotherapists to spread their knowledge in a scientific format, breaking barriers such as time constraints, inadequate resources, and geographical imbalances in therapeutic inputs (93). It is also a reminder that "lack of scientific evidence" does not equal "having evidence that an intervention has no therapeutic effect." Allied healthcare professionals are often burdened with demanding clinical responsibilities, and therefore, challenges in advance clinical research expose other inequalities such as insufficient support from professional bodies and workplaces, resistance to understanding classical interventions in neurorehabilitation, limitations in accessing training opportunities, or poor coordination between clinical and research positions. VT is an emerging topic in research, with 42 new scientific works in the last 3 years (2020–2023), in contrast with 36 articles published in the previous decade (2010–2019). The millennium was a turning point for physiotherapists to start publishing their works, with 15 articles between 2000 and 2009, while very few reports were published before that date.

Physiotherapy is a healthcare profession that, like surgery, operates in a manner reminiscent of a "craft apprenticeship." The global implementation of physiotherapeutic practices demands meticulous attention to the training standards of practitioners. Proficiency in hands-on techniques necessitates extensive personal and collaborative experiences, complemented by an in-depth and nuanced elucidation aligned with the continually evolving insights related to motor control. Classic physiotherapy interventions, which have demonstrated positive empirical outcomes, were originally articulated using the prevailing terminology at the time of their discovery. In some instances, practitioners simplified this wording to facilitate transmission within the hands-on training. Consequently, therapists may attain a consistent understanding of the theoretical underpinnings and proficiency in techniques at different times. Despite these variations, all therapists are entitled to access and receive support from research colleagues, ensuring the preservation of this knowledge as well as its publication in the appropriate format. Qualification and experience of the therapist can be found in the Supplementary material.

4.6 Limitations

The limited quality of evidence found for our analysis requires that the results be interpreted with caution. The scarcity and quality of studies, as well as the diversity of samples, control groups, and outcome measures, have made our evaluation difficult. Neuromodulation measurements have mostly been experimented with in healthy adults, although there are some in people living with MS, as well as two studies that measure physiological parameters in healthy children or those at neurological risk.

4.7 Future recommendations

Future studies aiming to broaden our understanding of the underlying mechanisms of VT must include larger and more diverse samples. Combining results in motor behavior as well as motor control in different conditions will also help us to understand the potentiality and limitations of this intervention, depending on the affected areas. This will put into the context of neuromodulation and neuroscience what we could initially only based on standard neurologic and neurophysiologic terms. Consistent outcomes and effects over medium- and long-term periods are also recommended, as are explicit descriptions of the intervention administered.

5 Conclusion

Although current evidence supporting VT is limited in quality, there are indications suggesting its potential usefulness for the treatment of respiratory, neurological, and orthopedic pathology. This systematic review and meta-analysis show the robustness of the neurophysiological mechanisms of VT, and that it could be an effective tool for the treatment of balance in adult neurological pathology. Neuromodulation of motor control areas has been confirmed by research focusing on the neurophysiological mechanisms underlying the therapeutic efficacy of VT.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JS-G: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. IS-E: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Conceptualization. MM-P: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Investigation, Conceptualization. VN-L: Writing – review & editing, Methodology, Formal analysis, Data curation. JS-M: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Investigation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1391448/full#supplementary-material

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Research hotspots and trends of microRNAs in spinal cord injury: a comprehensive bibliometric analysis

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Background: Spinal cord injury (SCI) is a nervous system disease leading to motor and sensory dysfunction below the injury level, and can result in paralysis. MicroRNAs (miRNAs) play a key role in SCI treatment, and related research provides insights for SCI diagnosis and treatment. Bibliometrics is an important tool for literature statistics and evaluation, objectively summarizing multidimensional information. This study comprehensively overviews the field through bibliometric analysis of miRNA and SCI research, providing contemporary resources for future collaboration and clinical treatment.

Materials and methods: In this study, we searched the Web of Science Core Collection (WOSCC) database. After careful screening and data import, we extracted annual publications, citation counts, countries, institutions, authors, journals, highly cited articles, co-cited articles, keywords, and H-index. Bibliometrics and visualization analyses employed VOSviewer, CiteSpace, the R package "bibliometrix," and online analytic platforms. Using Arrowsmith,[1] we determined miRNA-SCI relationships and discussed potential miRNA mechanisms in SCI.

Results: From 2008 to 2024, the number of related papers increased annually, reaching 754. The number of yearly publications remained high and entered a period of rapid development. Researchers from 50 countries/regions, 802 institutions, 278 journals, and 3,867 authors participated in the field. Currently, China has advantages in the number of national papers, citations, institutions, and authors. However, it is necessary to strengthen cooperation among different authors, institutions, and countries to promote the production of important academic achievements. The research in the field currently focuses on nerve injury, apoptosis, and gene expression. Future research directions mainly involve molecular mechanisms, clinical trials, exosomes, and inflammatory reactions.

Conclusion: Overall, this study comprehensively analyzes the research status and frontier of miRNAs in SCI. A systematic summary provides a complete and intuitive understanding of the relationship between SCI and miRNAs. The presented findings establish a basis for future research and clinical application in this field.

1 http://arrowsmith.psych.uic.edu

KEYWORDS
spinal cord injury, miRNAs, bibliometrics, inflammation, nerve

Introduction

Spinal cord injury (SCI) is a disease of the nervous system that can lead to motor and sensory dysfunction below the injury level, and even paralysis (1). About 250,000–500,000 people suffer from this disease annually worldwide (2, 3). The lifetime treatment cost for each SCI patient in the United States is about $500,000 to $1 million, with annual costs exceeding $7 billion (4, 5). Patients experience significant physical and psychological pain, making SCI a major societal burden. The pathophysiological development of SCI is complex, involving cell death, axonal injury, glial scar formation, inflammation, and more (6). However, current clinical treatment effects are very limited, and there is no cure yet, making SCI a major focus of research.

MicroRNAs (miRNAs) are endogenous small single-stranded non-coding RNA molecules (18–25 nucleotides) that can bind to target messenger RNA (mRNA) molecules to interfere with translation (7, 8). As key regulatory factors of transcriptional gene expression changes in nervous system diseases, miRNAs have been widely concerned and studied by researchers (9). During SCI development, miRNA regulates neuronal plasticity, degeneration, axon regeneration, and myelin regeneration by changing gene expression (10, 11). Research shows miR-940 decreases after SCI, and miR-940 overexpression inhibits inflammation and promotes functional recovery (12). Another study showed miRNA-124 inhibits neuronal apoptosis and induces functional recovery in SCI rats (13). Clarifying miRNAs' role in SCI pathophysiology is of great scientific significance for solving nerve regeneration and functional repair problems in patients.

Bibliometrics is an important tool for literature statistics and evaluation. By combining qualitative and quantitative analysis, this method can objectively and intuitively summarize multidimensional information (14). VOSviewer and CiteSpace are two popular bibliometric software (15, 16), which provide an overall view of basic data and dynamic trends. Research trends and hotspots in a field can be better explored and grasped by researchers through bibliometrics studies. Though there have been an increasing number of such studies with enhancement in bibliometrics visualization tools and research depth in recent years, no bibliometrics studies have focused on the role of miRNA in SCI.

Currently, a plethora of studies have explored the mechanistic relationship between miRNA and SCI, laying the foundation for clinical translation of SCI treatment. This study provides a comprehensive overview of the field through bibliometric analysis of miRNA and SCI research, enhancing overall understanding of researchers and providing contemporary resources for future collaboration and clinical treatment.

Materials and methods

Data sources and search strategies

In this study, we searched the Web of Science Core Collection (WOSCC) database, which contains a large number of documents in the biomedical field. The search used the following formats: TS = (microRNA*) AND TS = (Spinal cord injury). The time span was January 1, 2008 to January 31, 2024. After carefully searching the existing literature, we screened out 1,087 potential articles. We limited the types of articles to Article and limited the language to English, finally including 754 articles (Figure 1).

Data collection and statistics

Search results are downloaded in a "plain text file" format, with complete records and references in the WOSCC database. Data are extracted after careful screening and importing into Microsoft Excel 2016 for analysis: annual publications, citation numbers, countries, institutions, authors, journals, highly cited articles, co-cited articles, keywords, and H-index. The summarized data are imported into the online bibliometrics analysis platform,[2] and a fitting curve is used to predict the number of published documents.

Bibliometric analysis

To analyze the bibliometrics of SCI and miRNA, we visually analyzed selected data. These data clarified research trends, influence, and distribution. This paper used VOSviewer software for visual analysis of authors, keywords, keyword co-occurrence timeline, density maps, journals, highly cited literature, and co-cited literature. CiteSpace software was used for detailed visualization of countries/regions cooperation network map, institutions cooperation network map, strongest citation burst, keyword clustering, journal dual graph overlay, etc. The node size represents the number of nodes; the lines between nodes represent cooperation between institutions, with thicker lines indicating closer relationships. From these results, inferences about relationships between research hotspots and frontiers were made.

Analysis of the potential mechanisms based on the Arrowsmith project

Arrowsmith (see text footnote 1) was utilized to identify relationships between miRNAs and SCI and evaluate potential miRNA mechanisms in SCI. Keywords filtered through Arrowsmith served as prediction groups, while those filtered through VOSviewer were confirmation groups. Venn diagrams were drawn for both to determine potential keywords for miRNA and SCI research. R software was used for gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of

2 https://bibliometric.com/

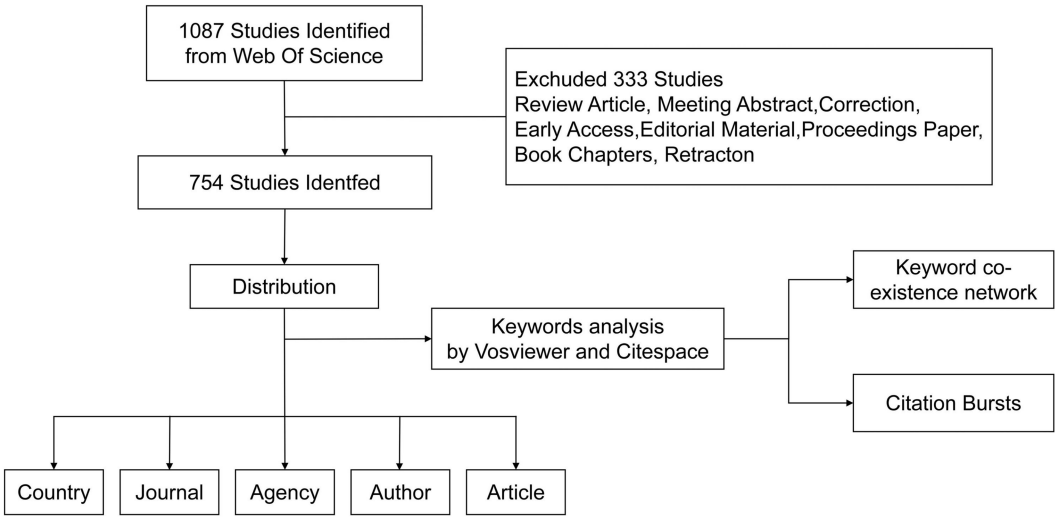

FIGURE 1
The inclusion and exclusion process of miRNAs in SCI research.

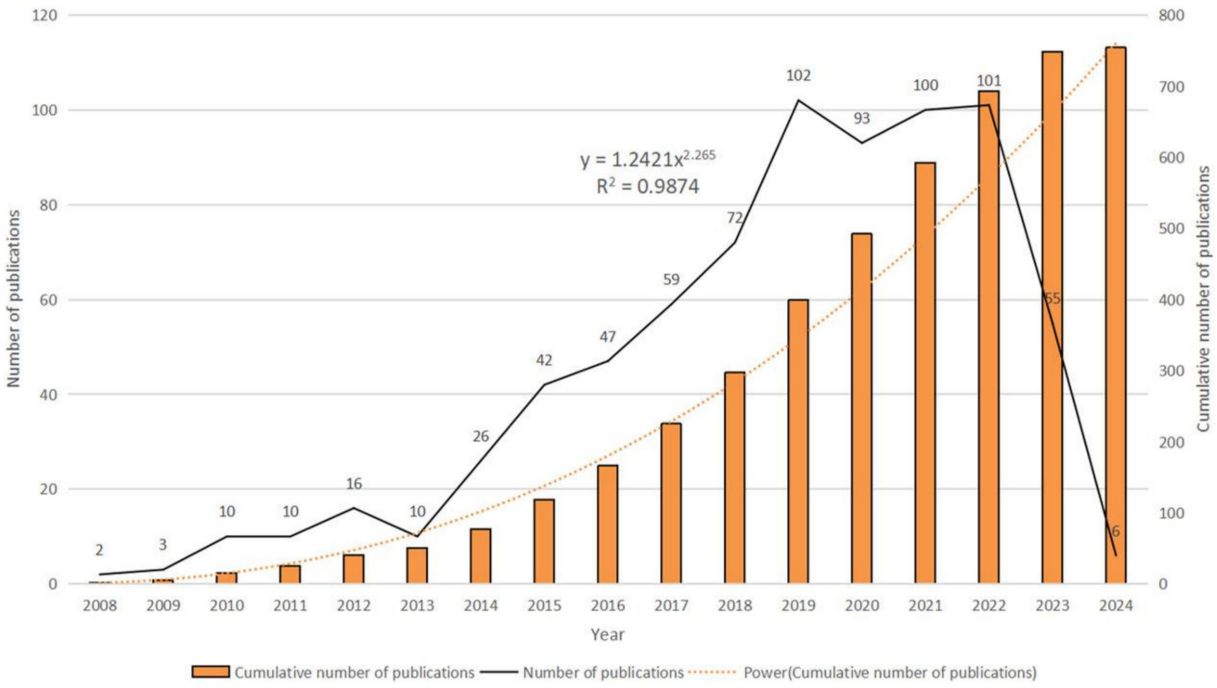

FIGURE 2
Annual publication volume and annual cumulative publication volume.

potential genes with correlation capacity ≥0.95. The STRING online database[3] was used to create a potential gene protein–protein interaction (PPI) network, visualized with Cytoscape software. Cytoscape software also aided in screening genes within the PPI network.

3 https://www.stringdb.org/

Results

Annual publications and trends

Analyzing publication trends enables understanding of the developmental speed and changing attention to miRNAs in SCI treatment (Figure 2). From 2008 to 2024, 754 papers were published. Annual publication numbers rapidly increased from 2013 to 2019, peaking in 2019 ($n = 102$). Publications in 2019–2022 were relatively flat,

but decreased significantly in 2023 ($n = 55$). With only January 2024 included, it is currently the year with the fewest publications ($n = 6$). The function formula of the fitting curve is "$y = 1.2421x^{2.265}$, $R^2 = 0.9874$," indicating the research growth curve in this field fits well. These results show studying miRNAs is an important direction in SCI.

Country/region analysis and international cooperation

We found that a total of 50 countries/regions have published literature on the role of miRNAs in SCI, with China being the most prominent country, accounting for the largest number of publications ($n = 527$; 59.48%) and citations ($n = 10{,}155$; 40.32%) (Figures 3A,B; Table 1). With the globalization of knowledge and technology, international cooperation is increasingly close, and the United States plays an important role in the cooperation network. European countries have the closest cooperation (Figure 3C). Overall, although China has the largest number of publications, it still lacks international cooperation and needs to strengthen exchanges in the future.

Institutional contribution

Papers in this field have been published by 802 institutions. Most of the top 10 universities in publication count and citation count are from China. China Medical University published the most articles ($n = 40$; 2.67%) and received the most citations ($n = 891$; 2.26%), ranking first in both categories (Figures 4A,B; Table 2). Johns Hopkins University ranks first in centrality (coefficient = 0.05), while Chinese research institutions rank relatively high, showing that Chinese universities have made remarkable achievements and great influence in the field of miRNAs related to SCI, but there is still room for improvement

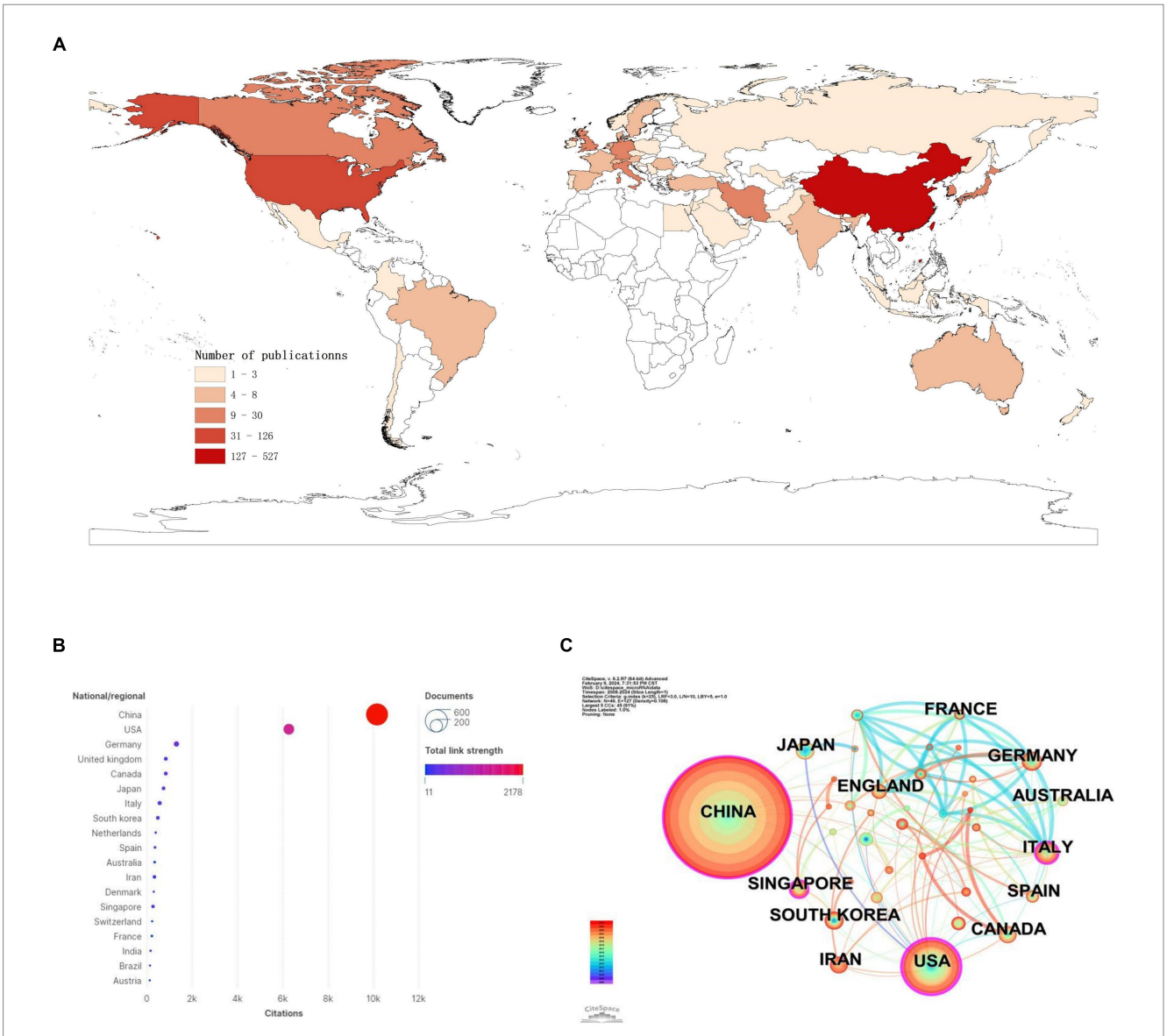

FIGURE 3
National/regional contributions of miRNAs and SCI-related research. **(A)** Comparative map of the cumulative number of papers published in each Countries/regions. **(B)** Countries/regions cited frequency bubble map. **(C)** Cooperation networks in countries/regions around the world.

TABLE 1 Top 10 countries/regions in terms of the number of documents and citations on miRNAs in SCI.

Rank	Country	Documents(%)	Rank	Country	Citations (%)
1	China	527 (59.48)	1	China	10,155 (40.32)
2	United States	126 (14.22)	2	United States	6,264 (24.87)
3	Germany	30 (3.38)	3	Germany	1,307 (5.19)
4	Italy	18 (2.03)	4	United kingdom	838 (3.32)
5	Canada	15 (1.69)	5	Canada	836 (3.31)
6	Japan	15 (1.69)	6	Japan	738 (2.93)
7	South Korea	15 (1.69)	7	Italy	567 (2.25)
8	United Kingdom	15 (1.69)	8	South Korea	485 (1.92)
9	Iran	13 (1.46)	9	Netherlands	391 (1.55)
10	Singapore	12 (1.35)	10	Spain	360 (1.42)

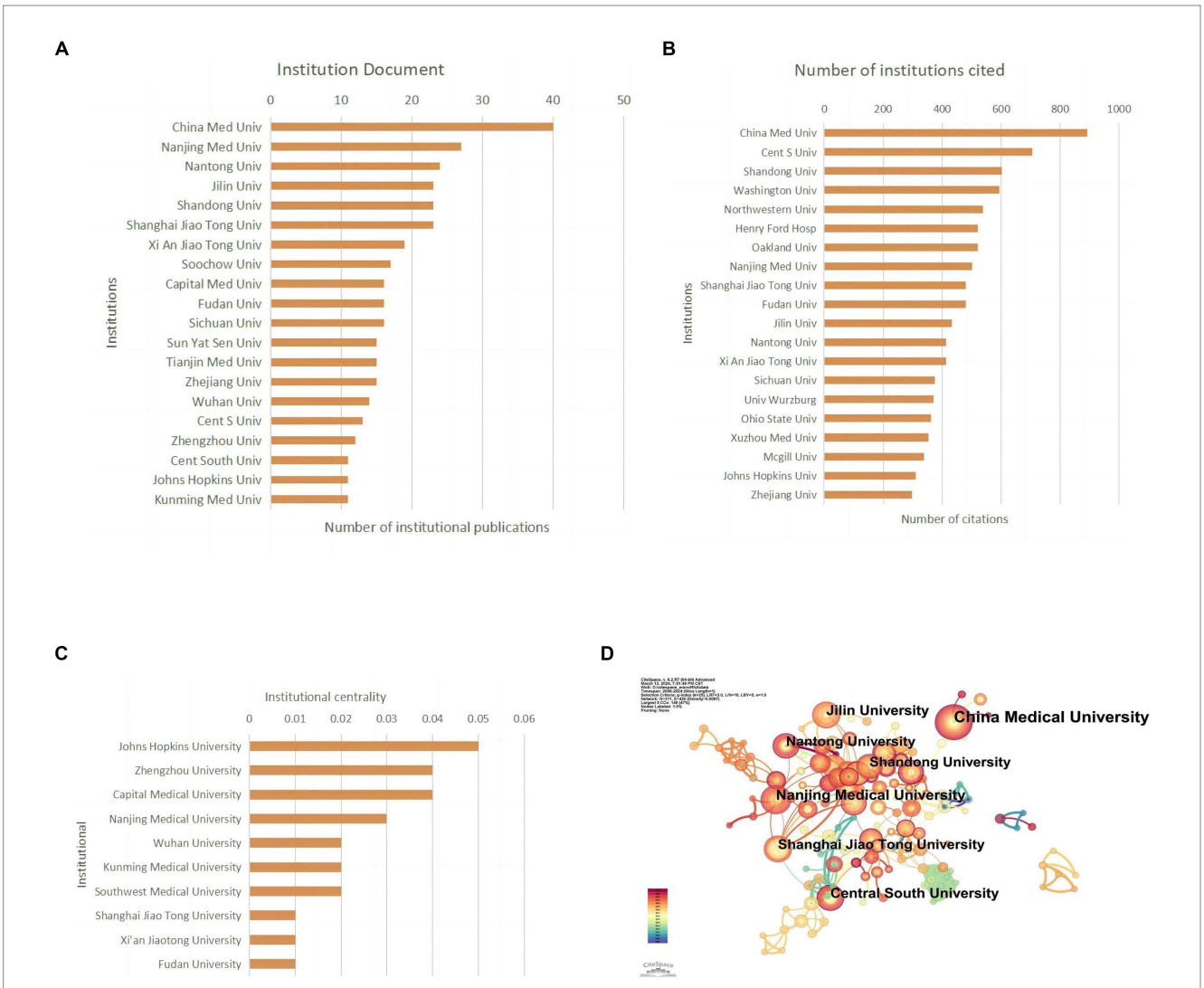

FIGURE 4
Institutional contribution on miRNAs in SCI research. **(A)** Top 10 institutions by publication volume. **(B)** Top 10 most cited institutions. **(C)** Top 10 intermediary centrality value of research institutions. **(D)** A visual network map of research institution contributions and collaborations.

(Figure 4C). Nevertheless, analyzing the scale and degree of inter-institutional collaboration reveals that institutions with more publications did not extensively collaborate with each other (Figure 4D).

Journal analysis

Related literature was published in 278 journals, with the most published article in European Review for Medical and Pharmacological

TABLE 2 Top 10 institutions in terms of the number of documents and citations on miRNAs in SCI.

Rank	Institution (n = 730)	Documents (%)	Rank	Institution (n = 730)	Citations (%)
1	China Med Univ	40 (2.67)	1	China Med Univ	891 (2.26)
2	Nanjing Med Univ	27 (1.80)	2	Cent S Univ	704 (1.79)
3	Nantong Univ	24 (1.60)	3	Shandong Univ	601 (1.52)
4	Shandong Univ	23 (1.53)	4	Washington Univ	593 (1.50)
5	Shanghai Jiao Tong Univ	23 (1.53)	5	Northwestern Univ	538 (1.36)
6	Jilin Univ	23 (1.53)	6	Henry Ford Hosp	521 (1.32)
7	Xi An Jiao Tong Univ	19 (1.26)	7	Oakland Univ	521 (1.32)
8	Soochow Univ	17 (1.13)	8	Nanjing Med Univ	502 (1.27)
9	Fudan Univ	16 (1.06)	9	Shanghai Jiao Tong Univ	480 (1.22)
10	Sichuan Univ	16 (1.06)	10	Fudan Univ	480 (1.22)

Sciences (n=25; 6.4%), the most cited journal in Experimental Neurology (n=715; 6.9%) (Figures 5A,B; Table 3), and the highest H-index in European Review for Medical and Pharmacological Sciences (Figure 5C). Considering journal classification and influence factors, research quality needs further improvement. Analysis of superimposed journal graphs shows yellow bars indicate articles in molecular/biology/immunology journals often cite articles in molecular/biology/genetics journals (Figure 5D). Per cooperative network analysis, journals fell into four clusters, with the large node/density of European Review for Medical and Pharmacological Sciences, Frontiers in Molecular Neuroscience, and Neural Regeneration Research indicating these journals' important roles in the field (Figures 5E,F).

Author contribution and collaboration analysis

A total of 3,867 authors have published relevant papers, with Ma, H publishing the most papers (n=11, 3.63%) and also being the most cited author (n=357, 4.68%), indicating extensive research in this field (Figures 6A,B; Table 4). Wang, Y, with the highest H-index, is the most influential author (Figure 6C). Many academic groups are active in this field, such as Ma, H, Feng, SQ, He, XJ, Lu, HB, etc. Authors within groups collaborate closely, but inter-group collaboration is insufficient (Figure 6D).

Analysis of highly cited articles and co-citation articles

Table 5 shows the top 10 cited publications, led by Xin HQ's article in Stem Cells, with 521 citations. It reported Mir-133b promotes neural plasticity and recovery post-stroke treatment via transfer of exosome-enriched particles. Liu NK's article in Experimental Neurology, "Altered microRNA expression post-traumatic spinal cord injury," was cited 153 times (Table 6). VOSviewer software is used to draw the visual map and visual density view of the cited documents and co-cited documents in order to obtain better visual effect. Only references with citation frequency ≥ 40 are shown in the cited chart. Xin (2013) was cited by more literatures (Figures 7A,B). Only references with citation frequency ≥ 30 are displayed in the co-cited reference map. Liu NK (2009) and Bartel Dp (2004) have attracted wide attention (Figures 7C,D).

Keyword analysis

Keywords are words that have a high degree of generalization of the overall research content of an article. Through co-occurrence analysis of 3,151 keywords in all literatures, it was found that research mainly focuses on SCI, expression, apoptosis, microRNAs, etc. (Figure 8A). The LLR algorithm was used to perform cluster analysis on all keywords, drawing a cluster map with a total of nine clusters. The smaller the classification number, the more keywords that classification contains. #0 neuropathic pain, #1 central nervous system; each tag is interrelated and developed, rather than existing independently (Figure 8B). According to keyword co-occurrence timeline chart of the references, this development and change can also be confirmed from 2018 to 2019, SCI related research content is the richest (Figure 8C).

Emergent words refer to keywords that appear within a short time or are used frequently reflecting a change in research direction within a field. Based on keyword intensity and duration research direction can be roughly divided into three stages: (1) 2008–2015 focusing on changes in RNA and related gene expression post spinal cord injury and stem cell therapy; (2) 2015–2018 focusing on peripheral nerve injury treatment and exploring in vivo SCI treatment in mice; and (3) 2018–2024 primarily studying extracellular vesicles for SCI repair and neuroinflammation alleviation. This development and change is also confirmed by the co-citation time chart of references. Keyword co-occurrence timeline reflects the richest SCI research content from 2018 to 2019 (Figure 8D).

Analysis of potential mechanisms based on the Arrowsmith project

We selected the keywords from the Arrowsmith project as the prediction group (n=2,779) and the keywords extracted by

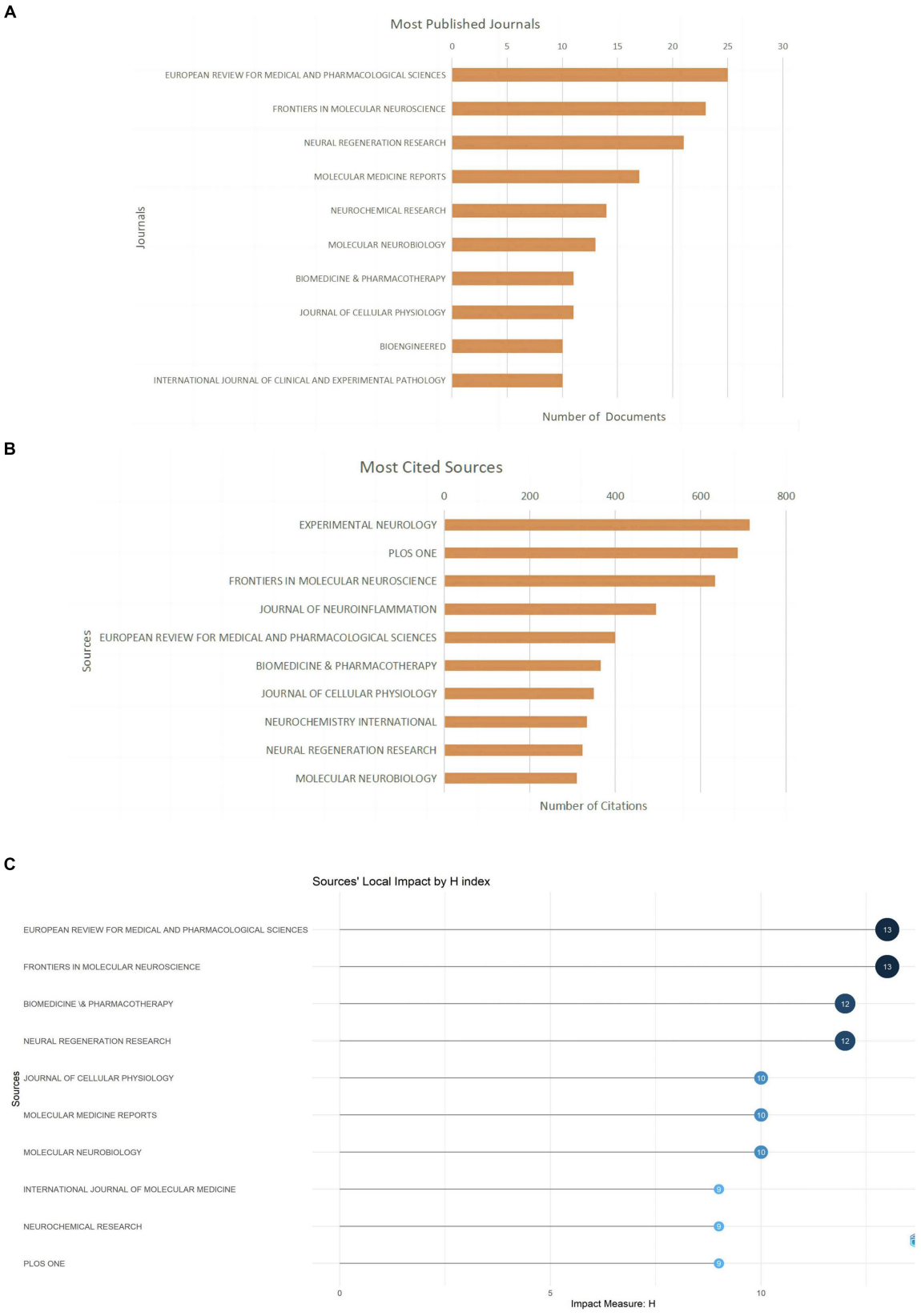

FIGURE 5 (Continued)

VOSviewer as the confirmation group ($n = 728$). A Venn diagram showed 204 common keywords, which can serve as potential research directions for studying miRNAs in SCI (Figure 9A). We extracted genes corresponding to these potential keywords for Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. The GO

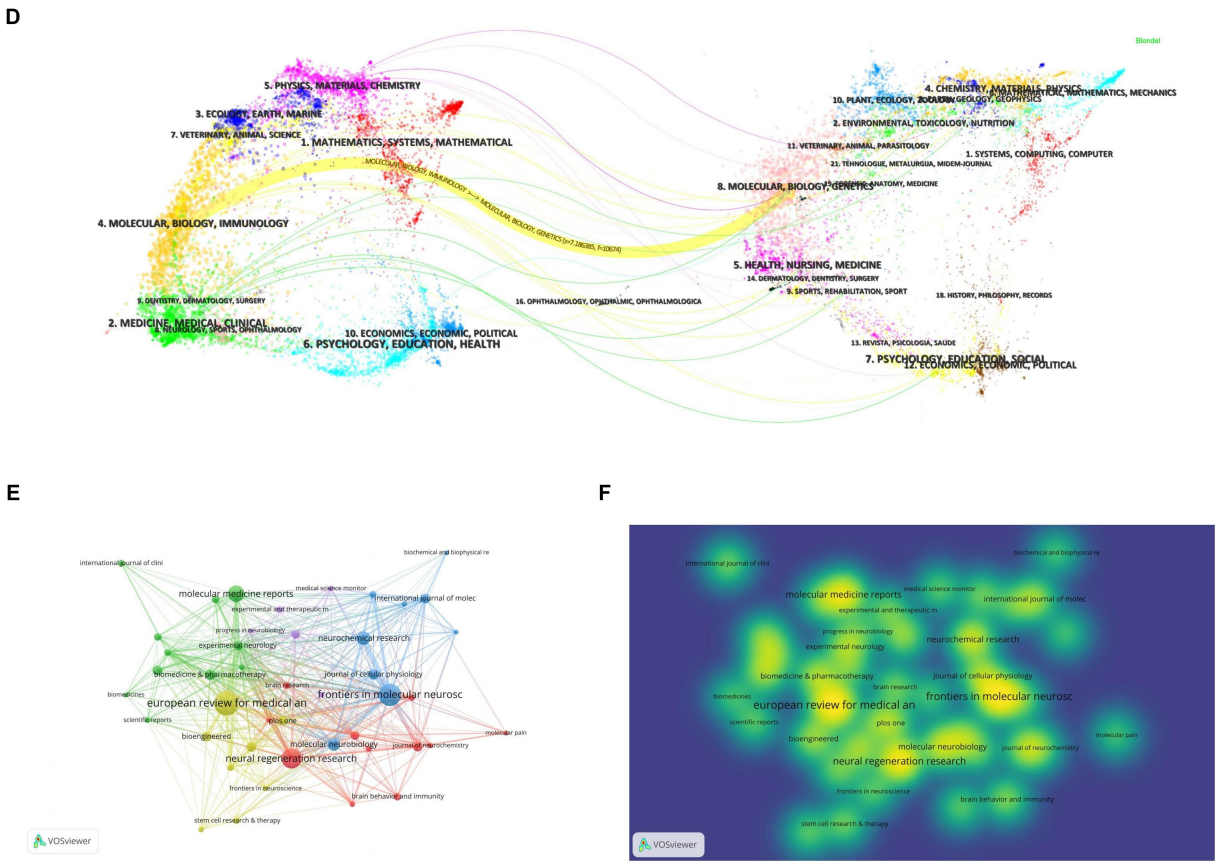

FIGURE 5
Journal characteristics of miRNAs and SCI-related research. **(A)** Top 10 journals by publication volume. **(B)** Top 10 most cited journals. **(C)** Top 10 journal H-index. **(D)** The dual-map overlay of journals in WOSCC. **(E)** Visual network map of core journals. **(F)** Visual density view of the core journals.

TABLE 3 Top10 journals in terms of the number of documents and citations on miRNAs in SCI.

Rank	Journals (n = 44)	Documents (%)	Rank	Journals (n = 44)	Citations (%)
1	European Review for Medical and Pharmacological Sciences	25 (6.4)	1	Experimental Neurology	715 (6.9)
2	Frontiers in Molecular Neuroscience	23 (5.8)	2	Plos One	687 (6.7)
3	Neural Regeneration Research	21 (5.3)	3	Frontiers in Molecular Neuroscience	634 (6.1)
4	Molecular Medicine Reports	17 (4.3)	4	Journal of Neuroinflammation	496 (4.8)
5	Neurochemical Research	14 (3.5)	5	European Review for Medical and Pharmacological Sciences	400 (3.9)
6	Molecular Neurobiology	13 (3.3)	6	Biomedicine & Pharmacotherapy	366 (3.5)
7	Biomedicine & Pharmacotherapy	11 (2.8)	7	Journal of Cellular Physiology	350 (3.4)
8	Journal of Cellular Physiology	11 (2.8)	8	Neurochemistry International	333 (3.2)
9	Bioengineered	10 (2.5)	9	Neural Regeneration Research	324 (3.1)
10	International Journal of Clinical and Experimental Pathology	10 (2.5)	10	Molecular Neurobiology	310 (3.0)

analysis showed biological processes (BP) focused on cell responses to hormones, oxidative stress, phosphorus metabolism, growth factors, and oxidative stress. Cellular components (CC) were mainly concentrated in receptor complexes, transcriptional regulatory complexes, and vesicle cavities. Molecular functions (MF) were remarkably rich in transcription factor binding and kinase binding (Figure 9B). KEGG pathway enrichment analysis showed the PD-1/PD-L1 signaling pathway played a certain role

FIGURE 6
Author contribution on miRNAs in SCI research. **(A)** Top 10 authors by publication volume. **(B)** Top 10 most cited authors. **(C)** Top 10 author H-index. **(D)** A visual network map of author contributions and collaborations.

(Figure 9C). A Protein–Protein Interaction (PPI) network was constructed and key genes were screened. It was found that AKT, MAPK, FOXO, and SMAD were potential targets related to miRNA treatment of SCI, indicating these genes played important roles in regulating cell pathophysiological processes. They are key players in SCI treatment (Figures 9D,E).

TABLE 4 Top 10 authors in terms of the number of documents and citations on miRNAs in SCI.

Rank	Author (n = 3,867)	Documents (%)	Total link strength	Rank	Author (n = 3,867)	Citations (%)	Total link strength
1	Ma, Hong	11 (3.63)	189	1	Ma, Hong	357 (4.68)	189
2	Feng, Shiqing	10 (3.30)	160	2	Ning, Bin	335 (4.39)	111
3	He, Xijing	10 (3.30)	44	3	Lu, Hongbin	279 (3.65)	89
4	Fang, Bo	9 (2.97)	179	4	Hu, Jianzhong	279 (3.65)	80
5	Ning, Bin	9 (2.97)	111	5	Li, Xiao-Qian	270 (3.54)	163
6	Cao, Yong	8 (2.64)	80	6	Fang, Bo	268 (3.51)	179
7	Li, Xiao-Qian	8 (2.64)	163	7	He, Xijing	228 (2.99)	44
8	Lu, Hongbin	8 (2.64)	89	8	Maza, Rodrigo M.	224 (2.93)	100
9	Wang, Tianyi	8 (2.64)	186	9	Munoz-Galdeano, Teresa	224 (2.93)	100
10	Yu, Bin	8 (2.64)	65	10	Nieto-Diaz, Manuel	224 (2.93)	100

TABLE 5 Top 10 highly cited articles on miRNAs in IDD in the WOSCC database.

Rank	Author	Title	Journal	Year	Citations
1	Xin, Hongqi	Mir-133b promotes neural plasticity and functional recovery after treatment of stroke with multipotent mesenchymal stromal cells in rats via transfer of exosome-enriched extracellular particles.	Stem Cells	2013	521
2	Mahar	Intrinsic mechanisms of neuronal axon regeneration.	Nature Reviews Neuroscience	2018	295
3	Sommer	Inflammation in the pathophysiology of neuropathic pain.	Pain	2018	278
4	Michell-robinson	Roles of microglia in brain development, tissue maintenance and repair.	Brain	2015	272
5	Liu, Nai-kui	Altered microRNA expression following traumatic spinal cord injury.	Experimental Neurology	2009	268
6	Bhalala	The emerging roles of microRNAs in CNS injuries.	Nature Reviews Neurology	2013	220
7	Saugstad	MicroRNAs as effectors of brain function with roles in ischemia and injury, neuroprotection, and neurodegeneration.	Journal of Cerebral Blood Flow and Metabolism	2010	202
8	Bhalala	MicroRNA-21 regulates astrocytic response following spinal cord injury.	Journal of Neuroscience	2012	183
9	Gaudet	MicroRNAs: roles in regulating neuroinflammation.	Neuroscientist	2018	170
10	Sun, Ping	MicroRNA-based therapeutics in central nervous system injuries.	Journal of Cerebral Blood Flow and Metabolism	2016	142

Discussion

Research progress on the effects of miRNAs on SCI

Spinal cord injury is a nervous system disease causing physical and psychological harm to patients and a heavy economic burden on society (17). It can be divided into primary and secondary injury. Primary injury is typically mechanical, while secondary injury can lead to insufficient perfusion of gray matter post-injury and spread to surrounding white matter (18, 19). Injury-induced oxidative stress, inflammation, glial or fibrotic scar formation, demyelination, and nerve injury can result in partial paralysis (20). Current research focuses on neuroprotection, neurorepair, and scar inhibition therapy. Neuroprotective therapies focus on reducing/preventing secondary damage (6). The goal of nerve repair therapy is to reshape neurovascular recovery of the nervous system (21). Scar inhibition is a potential strategy to control scar growth and promote axonal regeneration by inhibiting astrocyte proliferation and hypertrophy (22, 23). Current clinical treatments mainly involve surgical decompression and drug therapy. Surgical decompression can improve spinal cord compression, increase blood flow at the injury site, and reduce expansion. However, surgical treatment can lead to greater trauma and can only provide symptomatic relief rather than a fundamental cure (24, 25). Injectable drug therapy can also cause immune rejection, as well as excessive drug release and rapid degradation (26). In the context of medical treatment, the central objective is to mitigate hindrances to axon growth, ensuring a microenvironment that is conducive to nerve development. As part of this, there is an ongoing exploration of strategies that could potentially rebuild damaged neural circuits. Simultaneously, there is a concerted effort to promote functional recovery, enhancing the overall quality of life for patients. Lastly, there is a continuous search for suitable grafts that could support and guide the process of axon regeneration, ensuring optimal outcomes, miRNA-based therapy, blood vessel intervention and combination of multiple treatments will play a key role in the treatment of SCI in the future (27).

MicroRNAs are considered important biomarkers and therapeutic targets in SCI development (28). They exhibit tissue specificity and stability; miRNA content changes post-SCI are prerequisites for biological effects (29). MiRNAs serve as pathological biomarkers for

Alzheimer's disease, epilepsy, brain injury, and other conditions (30, 31). Bioinformatics analyses show abnormal miRNAs' potential target genes post-SCI involve SCI pathogenesis, including inflammation, oxidative stress, apoptosis, and neuronal death (32). They also impact astrocytes and scar formation (33). Research on miRNAs and SCI can inform SCI diagnosis and treatment, but miRNAs' pathophysiological significance remains incompletely determined. We use various bibliometrics tools for quantitative analysis, citation analysis, and visualization to reveal research hotspots and prospects. Compared to traditional review and meta-analysis, our approach explores research trends across multiple dimensions, providing richer, deeper, and more diversified information. It offers new reference and direction for SCI treatment and development.

General research trends on the role of miRNAs in SCI

Bibliometrics can systematically classify and analyze literatures on different topics, enabling better understanding of correlations between hot spots, trends, and topics within a research field (34). This study

TABLE 6 Top 10 co-citation articles on miRNAs in SCI in the WOSCC database.

Rank	Author	Title	Journal	Year	Citations
1	Liu NK	Altered microRNA expression following traumatic spinal cord injury.	Experimental Neurology	2009	153
2	Bartel DP	MicroRNAs: genomics, biogenesis, mechanism, and function.	Cell	2004	124
3	Bhalala OG	MicroRNA-21 regulates astrocytic response following spinal cord injury.	Journal of Neuroscience	2012	90
4	Hu JZ	Anti-apoptotic effect of microRNA-21 after contusion spinal cord injury in rats.	Journal of Neurotrauma	2013	87
5	Yunta M	MicroRNA dysregulation in the spinal cord following traumatic injury.	PloS One	2012	87
6	Strickland ER	MicroRNA dysregulation following spinal cord contusion: implications for neural plasticity and repair.	Neuroscience	2011	77
7	Basso DM	A sensitive and reliable locomotor rating scale for open field testing in rats.	Journal of Neurotrauma	1995	76
8	Ning B	MicroRNAs in spinal cord injury: potential roles and therapeutic implications.	International Journal of Biological Sciences	2014	67
9	Livak KJ	Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method.	Methods	2001	66
10	Bartel DP	MicroRNAs: target recognition and regulatory functions.	Cell	2009	65

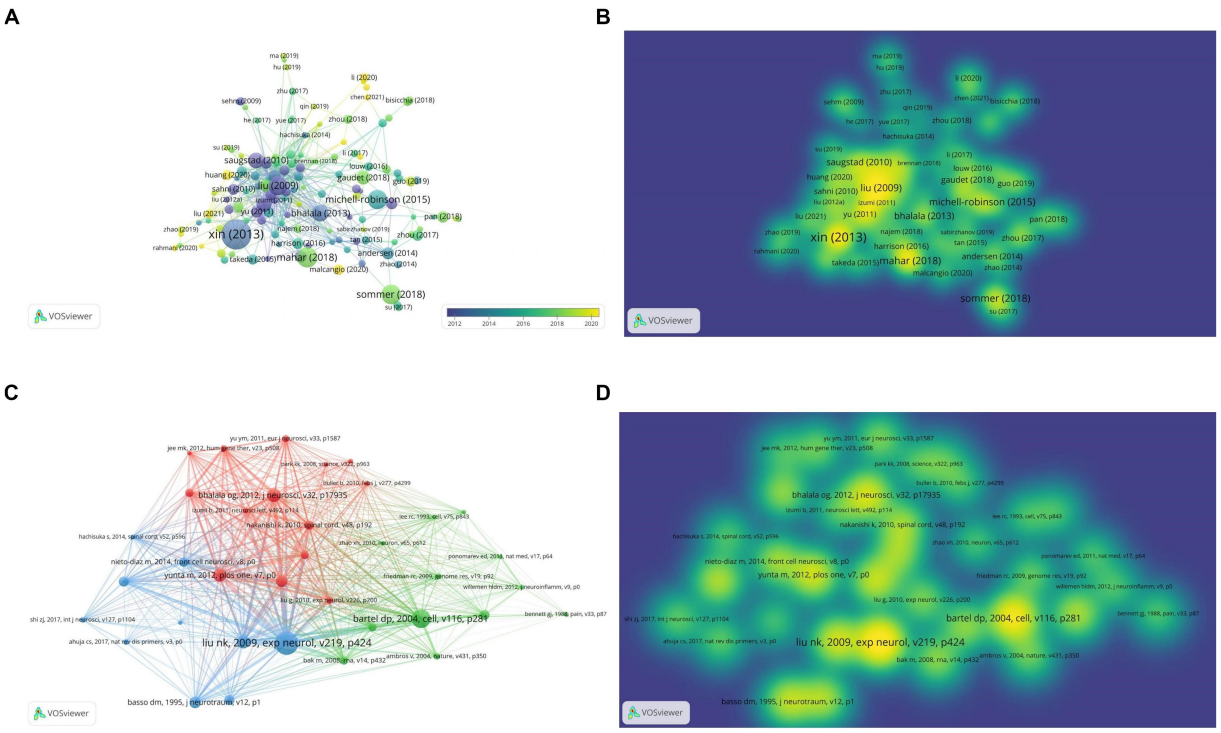

FIGURE 7
Characteristics of highly cited and co-citation articles on miRNAs and SCI. **(A)** Visual network diagram of the cited article. **(B)** Visual density view of the cited articles. **(C)** Visual network diagram of co-cited articles. **(D)** Visual density view of co-cited articles.

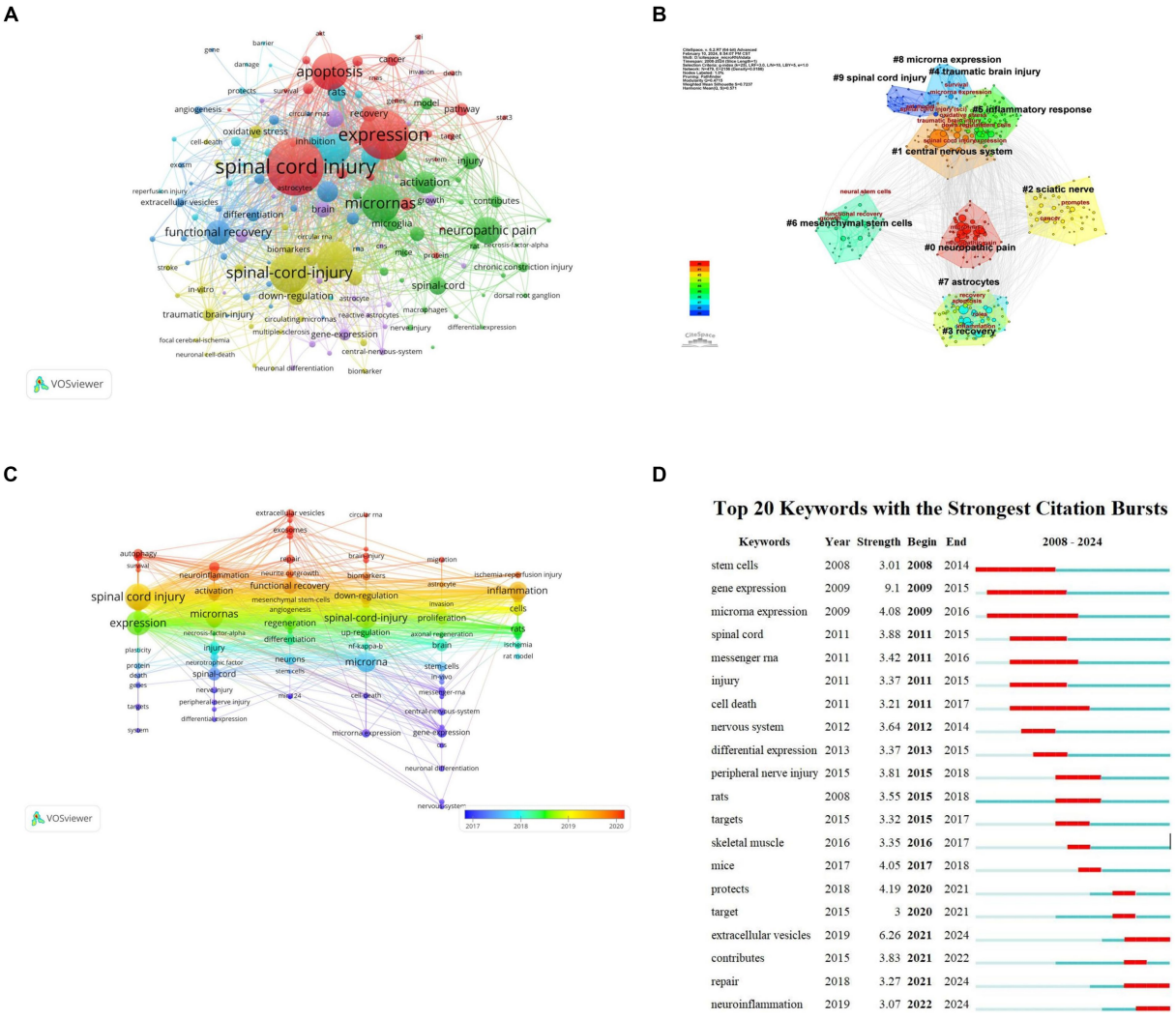

FIGURE 8
Keyword analysis of miRNAs and SCI research. **(A)** Keyword clustering network map. **(B)** Keyword clustering analysis. **(C)** Keyword co-occurrence timeline by keywords on miRNAs in SCI. **(D)** Top 20 Keyword with the strongest citation bursts on miRNAs in SCI.

applies bibliometrics methods to examine literature on miRNAs' role in SCI restoration. From 2008 to 2022, related literature rose yearly, totaling 754 articles. Publications remained high and entered rapid growth. Involving 50 countries/regions, 802 institutions, 278 journals, and 3,867 authors, indicating sustained researcher interest and a hot topic in SCI restoration.

China currently has clear advantages in terms of national paper count, citation count, institutional ranking, and author ranking. However, cooperative network analysis shows the United States occupies an important position in the cooperative network, with high H-index for research institutions, indicating the United States also plays an important role in promoting related work. China's overall link strength in the cooperation network remains insufficient; international exchanges and cooperation should be strengthened. Ma, H and Feng, SQ from China are field leaders and may continue to hold leadership positions, but their research teams are primarily domestically based. Journal research shows European Review for Medical and Pharmacsciences is the most published journal, also with the highest H-index, while Experimental Neurology is the most cited. Considering journal division and impact factors, research quality in this field needs further improvement. Chinese research institutions and scholars can advance miRNA research in SCI recovery by strengthening international cooperation, introducing advanced methods and technologies, critically evaluating and improving research papers, and actively participating in academic conferences. Such efforts can enhance academic level and reputation, and contribute important scientific achievements to the field.

Hotspots and research trends on the role of miRNAs in SCI

Cited and co-cited documents refer to research in which one document cites another, and multiple documents cite the same one, respectively (35). Research references help scholars understand hotspots and frontiers in a field, identify key documents with important value, reveal academic networks, and strengthen knowledge dissemination. Combining literature contents in Tables 5, 6, we found inflammation, neuron protection, axon

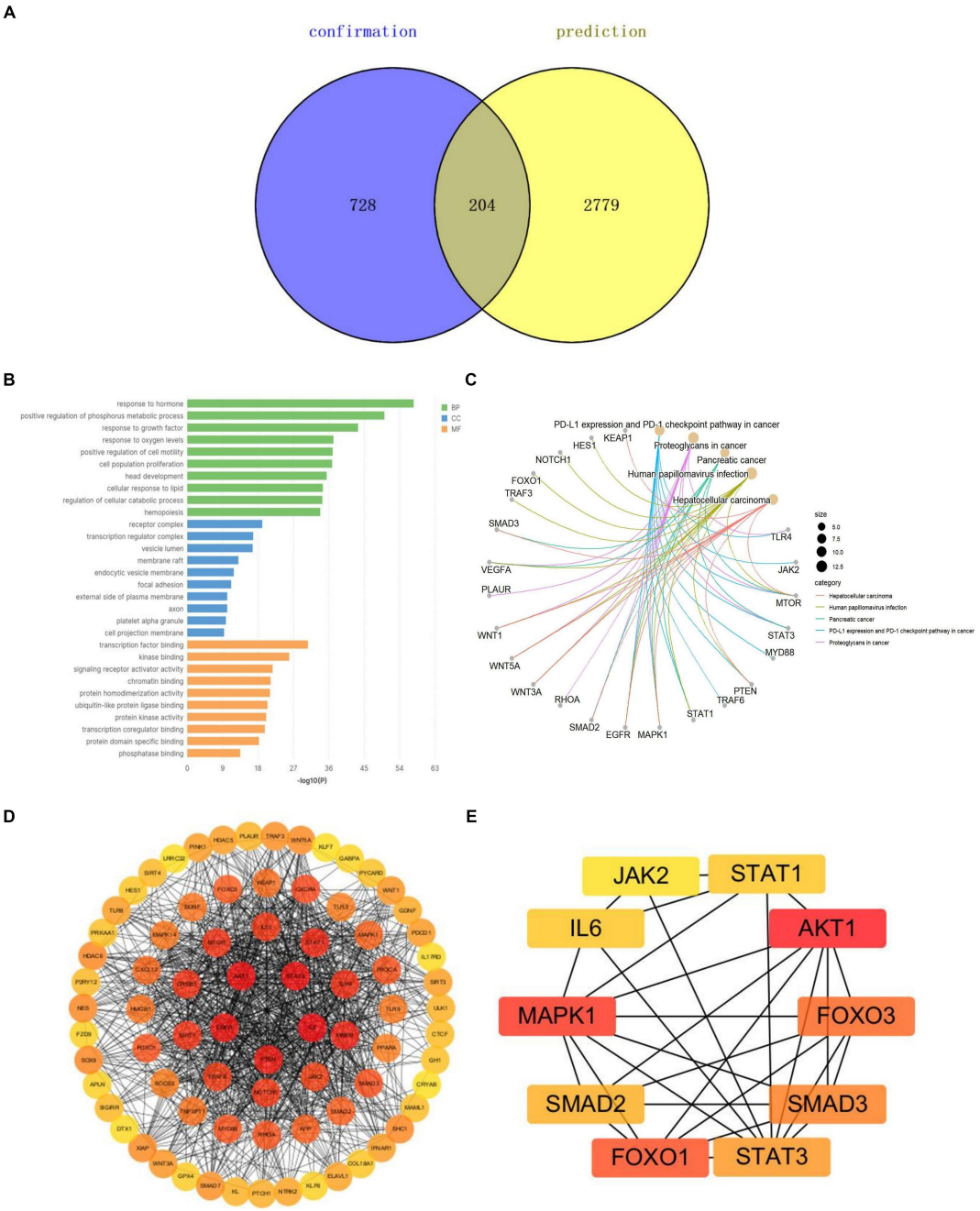

FIGURE 9
Potential keyword analysis of miRNAs and SCI research. **(A)** Venn diagrams for keywords of prediction and confirmation groups. **(B)** GO analysis of the potential key genes. **(C)** KEGG pathway enrichment analysis of the potential key genes. **(D)** PPI network of miRNA-related targets in SCI. **(E)** Hub genes of miRNA-related targets in SCI.

regeneration, scar formation, and specific mechanisms post-SCI remain research foci.

Keyword analysis extracts keywords or key phrases through processing and statistically analyzing large document, article, or data sets, enabling understanding of research topics, hotspots, and basic content. This study's keywords are spinal cord injury, expression, apoptosis, and miRNAs. Changes in miRNA gene expression lead to increased apoptosis and improved SCI. This strategy remains a hot research topic. miR-7a treats SCI by inhibiting neuronal apoptosis and oxidative stress (36), while miR-487b inhibits inflammation and neuronal apoptosis in SCI by targeting Ifitm3 (37). Based on keyword cluster analysis, nerve injury closely relates to inflammation. Currently, combined with keyword co-occurrence timeline and Reference citation bursts, keywords gradually transition to extracellular vesicles and neuroinflammation. Long et al. reported astrocyte-derived exosomes rich in miR-873a-5p inhibit neuroinflammation post-traumatic brain injury through microglial phenotypic regulation (38). Future directions include exosomes carrying miRNAs to inhibit inflammation for SCI treatment.

According to GO analysis and KEGG pathway, miRNAs actively participate in pathophysiological activities post-SCI. The PD-1/PD-L1

signaling pathway is involved in inhibiting neuroinflammation and improving traumatic brain injury (39). PPI network predicts AKT, MAPK, and FOXO as important pivotal genes, potentially key in apoptosis, autophagy, and inflammation. Currently, these genes are widely studied in SCI research. miR-21-5p, miR-92b-3p, and miR-34a all inhibit neuronal apoptosis and promote nerve regeneration via AKT (40–42). Excessive miR-340-5p reduces spinal cord injury-induced neuroinflammation and apoptosis by modulating P38-MAPK signaling (43). FOXO is widely reported in anti-inflammatory and anti-cancer studies (44, 45). SMAD plays an important role in SCI remyelination (46). Elucidating miRNA-target gene regulatory mechanisms may achieve reliable therapeutic effects and more comprehensive, effective rehabilitation programs for SCI patients.

Prospects of therapeutic of miRNAs in SCI

At present, effective clinical treatment methods for SCI remain lacking, and emerging treatment methods such as cell transplantation, epigenetic regulation, artificial scaffold transplantation, and gene therapy are the main research directions for researchers (47, 48). Secondary injury usually leads to changes in the spinal cord microenvironment, resulting in changes in miRNA expression (49). This discovery provides potential opportunities for gene intervention (50). MiR-33-5p alleviates rat SCI and protects PC12 cells from lipopolysaccharide-induced apoptosis (51). MiR-433-5p overexpression protects against acute spinal cord injury by activating MAPK1 (52). MiR-7a improves spinal cord injury by inhibiting neuronal apoptosis and oxidative stress (36). Although the use of miRNAs as a therapeutic agent has attracted considerable attention due to its therapeutic effect on SCI, The limitations of using miRNAs as a therapeutic tool lie in their delivery and activation *in vivo* (29).

Exosomes, as intercellular communication carriers, play an irreplaceable role in maintaining multicellular organism functional integrity. Protected by a phospholipid layer, miRNAs can be accurately transported to target sites and avoid hydrolysis by extracellular enzymes, enhancing blood–brain barrier penetration and preventing misdelivery. Jiang et al. (53) confirmed neuron-derived exosome-delivered miR-124-3p protects spinal cord from traumatic injury by inhibiting neurotoxic microglia and astrocyte activation. Liu et al. (54) demonstrated hypoxic-preconditioned mesenchymal stem cell-derived exosome shuttle miR-216a-5p repaired traumatic spinal cord injury by altering microglia M1/M2 polarization. Recent miRNA delivery technology advances raise high expectations for miRNA therapeutics. While no clinical trials yet use exosome-attached miRNAs to treat human SCI, experimental data strongly support this approach's feasibility. We must further analyze its beneficial effects and potential risks before applying it clinically.

Limitations

This study, for the first time, conducted systematic bibliometric and visual analysis on miRNA and SCI-related documents extracted from the WOSCC database. Based on the Arrowsmith project, we also revealed potential mechanisms between miRNA and SCI. The study's results laid a foundation for further research in this field. However, the study also has limitations. First, the included database data is relatively simple, and some other data may be ignored. Additionally, excluding articles not in English may impact conclusions. The database used for this study is updated in real-time and does not include papers published after the search date, which may result in differences between results at publication time and this result.

Conclusion

The study highlights the global research interest, development trends and future clinical application potential of miRNAs in SCI treatment. We have confirmed the key role of miRNA in spinal cord injury and it has garnered continuous attention from researchers, becoming a hotspot of research in this field. Since 2008, annual publications in this field have increased. China leads in publication quantity, research institutions, and authors, but requires strengthened international collaboration. Current research focuses have shifted from single miRNA treatments to SCI treatment using exosome-attached miRNAs. In mechanism research, AKT, MAPK, FOXO, and SMAD are potential targets of miRNAs influencing SCI. There are relatively few clinical studies on miRNAs in SCI treatment. However, large-scale, multicenter clinical trials are needed to prove treatment effectiveness and safety.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

BH: Methodology, Resources, Writing – original draft. YZ: Software, Visualization, Writing – original draft. CC: Conceptualization, Writing – original draft. BW: Investigation, Writing – original draft. HZ: Data curation, Writing – review & editing. BL: Supervision, Writing – review & editing. RZ: Validation, Writing – review & editing. FF: Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neurorehabilitation with vagus nerve stimulation: a systematic review

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Objective: To systematically review vagus nerve stimulation (VNS) studies to present data on the safety and efficacy on motor recovery following stroke, traumatic brain injury (TBI), and spinal cord injury (SCI).

Methods: Data sources: PubMed, EMBASE, SCOPUS, and Cochrane.

Study selection: Clinical trials of VNS in animal models and humans with TBI and SCI were included to evaluate the effects of pairing VNS with rehabilitation therapy on motor recovery.

Data extraction: Two reviewers independently assessed articles according to the evaluation criteria and extracted relevant data electronically.

Data synthesis: Twenty-nine studies were included; 11 were animal models of stroke, TBI, and SCI, and eight involved humans with stroke. While there was heterogeneity in methods of delivering VNS with respect to rehabilitation therapy in animal studies and human non-invasive studies, a similar methodology was used in all human-invasive VNS studies. In animal studies, pairing VNS with rehabilitation therapy consistently improved motor outcomes compared to controls. Except for one study, all human invasive and non-invasive studies with controls demonstrated a trend toward improvement in motor outcomes compared to sham controls post-intervention. However, compared to non-invasive, invasive VNS, studies reported severe adverse events such as vocal cord palsy, dysphagia, surgical site infection, and hoarseness of voice, which were found to be related to surgery.

Conclusion: Our review suggests that VNS (non-invasive or invasive) paired with rehabilitation can improve motor outcomes after stroke in humans. Hence, VNS human studies are needed in people with TBI and SCI. There are risks related to device implantation to deliver invasive VNS compared to non-invasive VNS. Future human comparison studies are required to study and quantify the efficacy vs. risks of paired VNS delivered via different methods with rehabilitation, which would allow patients to make an informed decision.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=330653.

KEYWORDS

vagus nerve stimulation, stroke, brain injury, spinal cord injury, rehabilitation, motor activity vagus nerve stimulation, spinal cord injury stroke, motor activity

Introduction

Approximately one million people suffer from stroke, traumatic brain injury (TBI), and spinal cord injury (SCI) in the United States alone, resulting in significant disability due to loss of functional abilities required to live independently, such as transfers and activities of daily living (1–5). Specifically, severe impairment in arm/hand motor function requires significant assistance and caregiver support, resulting in enormous lifetime direct and indirect costs (6–12). Various approaches to improve upper extremity motor function after stroke, TBI, and SCI include standard rehabilitation therapy focusing on strengthening, stretching, and task-specific movement therapy with or without biofeedback, robotic therapy, functional electrical stimulation, constraint-induced movement therapy, and reconstructive surgeries (13–20). However, recovery is challenging; even after completing conventional rehabilitation therapies, people frequently have residual motor disabilities following stroke, TBI, and SCI. It is clear that additional facilitation of neuroplastic change is required to achieve a drastic shift in the rehabilitation status quo (21).

Neuroplasticity is the capacity of spared neural cells and pathways to change in response to intrinsic and extrinsic factors aiding motor recovery after neurological injury (22–24). Hence, in the last decade, there has been an interest in pairing rehabilitation therapy with various neuromodulation interventions, including vagus nerve stimulation. The vagus nerve can be stimulated via external electrodes placed over either the auricular branch or cervical branch non-invasively or invasively via direct electrode placement over a cervical branch of the vagus nerve over the anterior aspect of the neck. The pairing of vagus nerve stimulation (VNS) with movement or sensory input for generating targeted neuroplasticity has demonstrated a potential for clinical application (25–34). The vagus nerve is an important cranial nerve that carries parasympathetic and brachial motor efferents to several target organs, and a large proportion of vagus nerve fibers also consists of afferent connections to several nuclei in the brain stem. These connections regulate the release of neuromodulators, including acetylcholine, norepinephrine, serotonin, and brain-derived neurotrophic factors, which promote cortical plasticity (30, 31, 35–39).

Several studies have been conducted in animals and humans to explore the promising effects of VNS on motor recovery following a neurological injury. However, there is heterogeneity in the study population, mode and location of VNS, stimulation parameters, timing of stimulation when combined with rehabilitation therapy, and lack of consistent reporting on safety and adverse events. It is essential to systematically analyze and review pre-clinical and clinical data to understand the underlying mechanism, principles, and safety; to identify the gaps to fill prior to rapid clinical translation of VNS for motor recovery. In one of the recently published systematic reviews on VNS in the stroke population (40), results from non-invasive and invasive studies were combined when the meta-analysis was performed. It is not ideal to combine study results from non-invasive and invasive VNS studies due to differences in methods of stimulation and mechanisms; the experts in the field of VNS expressed similar views on this review paper in a recent publication (41).

To fill these gaps in the literature, we performed an overarching complete review of the safety and efficacy of VNS on motor recovery following neurological injury in animals and humans.

We performed a quantitative synthesis of primary motor outcomes reported in invasive and non-invasive VNS human RCTs, separately utilizing a novel method recently published in two prestigious journals, which provides an estimate of relative improvement in the intervention group compared to controls. The relative improvement is a critical estimate, allowing readers to compare improvements of non-invasive and invasive VNS, and to determine if the additional benefit is worth the risk associated with surgical implantation of VNS devices based on current evidence. Finally, we provided a detailed account of adverse events reported in these studies and the cumulative incidence of each type of adverse event when data was available.

Methods

This systematic review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. It was pre-registered with the PROSPERO prospective register of systematic reviews (CRD42022330653).

Search strategy and inclusion criteria

We conducted a literature search on PubMed, EMBASE, SCOPUS, and Cochrane Central Register of Controlled Trials using search terms: "vagus nerve stimulation," "stroke," "brain injury," and "spinal cord injury." We included all clinical trials (both randomized and non-randomized) of vagus nerve stimulation in animal models and humans with stroke, TBI, and SCI published between 1 January 2002 and 15 May 2022, focusing on the effects of VNS on motor recovery.

Data extraction

Two authors independently reviewed all abstracts found from the above search strategy and screened the abstracts for eligibility using similar criteria for animal and human studies. After removing duplicates, two authors (RK and AM) reviewed 200 abstracts and excluded studies that did not meet eligibility criteria (Figure 1). After identifying eligible papers through abstract review, authors RK, AM, and NY reviewed full texts for final inclusion and data extraction. We also excluded studies that did not assess the effects of VNS on motor recovery and did not report any motor or functional outcomes as primary or secondary outcome measures. Desired data was extracted in electronic data collection forms. Data elements included detailed information on demographics, diagnosis, study design, intervention, controls, and outcome measures (Tables 1, 2). We also collected detailed information on the effects of VNS compared to controls on motor and functional outcome measures.

Data synthesis

We provided a qualitative description of the effects of VNS on outcomes and summarized the data separately for animal and human

Abbreviations: VNS, Vagus nerve stimulation; TBI, Traumatic Brain Injury; SCI, Spinal Cord Injury.

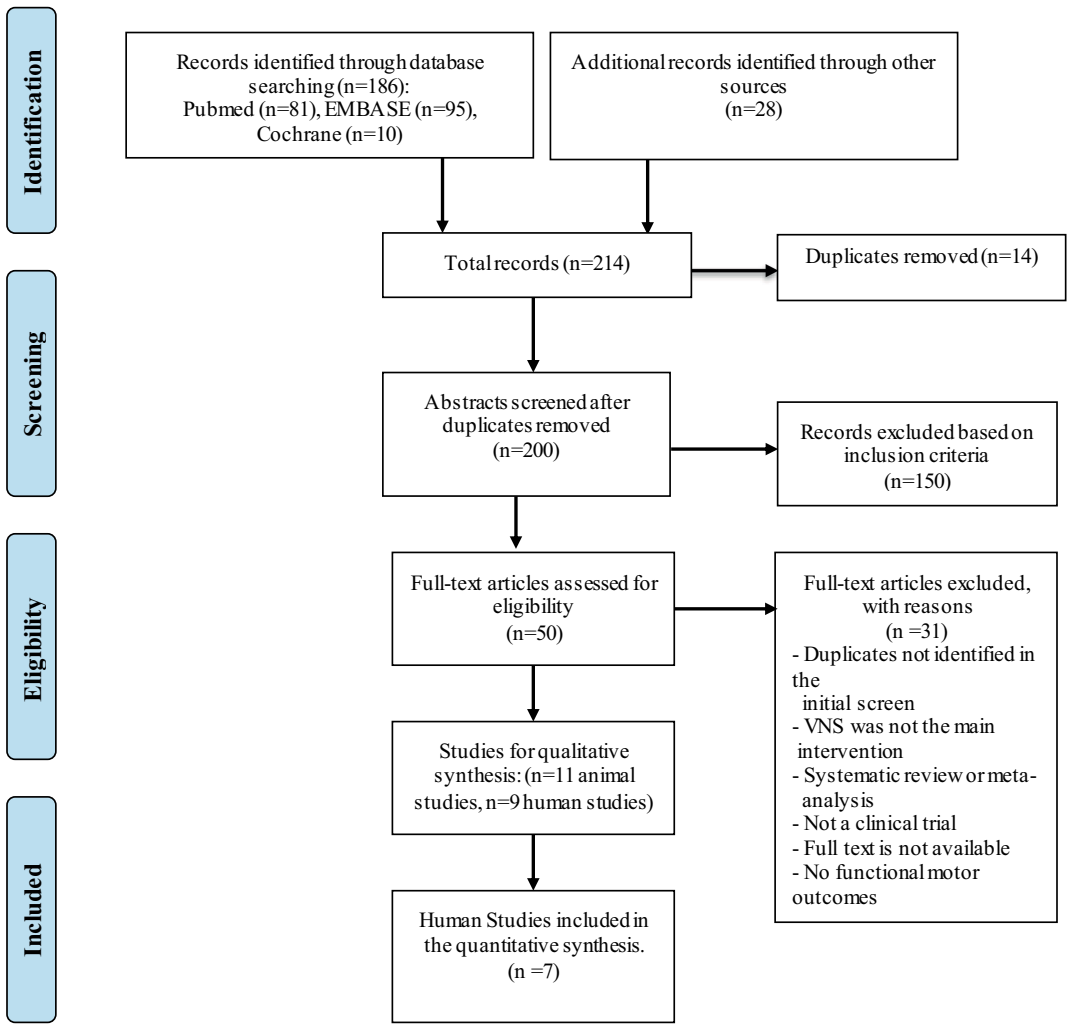

FIGURE 1
PRISM flow diagram.

studies in Tables 1, 2, respectively. We also included the results of primary outcome data from human RCTs in Table 3. We reported the results of all functional motor outcomes in Tables 1, 2 if provided in the literature. We summarized the results in tables based on a previously used method by our research team in a recent systematic review. The characters "+S" or "0" were used to indicate whether a particular outcome measure achieved statistical significance, with "+S" in favor of VNS therapy, or "0" if there was no difference between active VNS and control groups (42). We did not perform a meta-analysis due to high variability in the methods used for VNS, and our team considered it would not provide an accurate effect size (43). VNS experts expressed similar concerns about the inappropriateness of combining results from various stimulation methods, published in a commentary (41). Hence, we calculated the relative change in outcome measures to assess the efficacy of VNS therapy on the most widely used upper extremity motor outcome measure, the upper extremity Fugl-Meyer-Assessment (FMA-UE), separately for non-invasive and invasive studies utilizing methods in two recently published systematic review papers (42, 44).

The relative change for outcome measure FMA-UE was obtained after subtracting the pre-post change in FMA-UE score in the active VNS group from the pre-post change in FMA-UE score in the control group, divided by the average baseline FMA-UE score of the VNS group. This relative difference or change estimates the percentage improvement or worsening of the FMA-UE score in the VNS group relative to the control group. We also calculated the median (IQR) for the mean improvement in upper extremity-FMA scores in the VNS group compared to the control group for human studies.

Risk of bias

Human studies included in relative change calculations were appraised for risk of bias using the ROBIN-II tool for RCTs (45). Detailed appraisal report is outlined in Supplementary material and the overall risk of bias for the appraised studies is reported in Table 3.

Results

Based on our literature search criteria, we identified 11 VNS studies on motor recovery in animal models and 8 in humans

TABLE 1 Invasive VNS animal studies.

Study and study design	Animal species/ Gender	Lesion	Sample size	Control	Active intervention	Frequency and duration	Motor outcomes measures (T1 = baseline, T2: post-intervention, T3: f/u)	Results-motor outcomes
Stroke studies								
Khodaparast, 2013 (control trial)	4 months old Female Sprague–Dawley Rats	Unilateral motor cortex ischemic lesion of M1	■ Paired VNS = 9 ■ Control = 9	Only RT: Isometric force task training	Paired VNS to left CVN, delivered on successful trials with RT	30 min twice daily or 5 days/ week for 5 weeks	Peak force, Hit rate at T1, T2 and T3 at 1 week	Paired VNS vs. control +S at T2 and T3
Khodaparast, 2014 (control trial)	Adult Female Sprague–Dawley Rats	Unilateral ischemic lesion -left M1	■ Paired VNS = 8 ■ Control = 9 ■ Delayed VNS = 3	Only RT: Bradykinesia task	Paired VNS to left CVN stims delivered on successful trials with RT Delayed VNS (1): every 12 s for 1 h received 2 h after RT	30 min twice daily for 5 days/ week for 5 weeks	Hit rate at T1 and T2	■ Paired VNS vs. control: +S ■ Delayed VNS vs. control: 0
Hays, 2014 (control trial)	4 months old Female Sprague–Dawley Rats	Unilateral motor cortex ischemic lesion of M1	■ Paired VNS = 8 ■ Extra VNS = 6 ■ Delayed VNS = 7 ■ Control: 10	Only RT: Isometric force task training	Paired VNS to left CVN on successful trials with RT Delayed VNS: every 10 s for 1 h, 2 h after RT Extra VNS: VNS during RT at an average every 2 s	30 min twice daily for 5 days/ week for 5 weeks	Maximum pull force and hit rate at T1 and T2.	■ Paired VNS vs. control: +S ■ Extra VNS vs. control: +S ■ Delayed VNS vs. control: +S ■ Paired VNS superior to delayed and Extra VNS (+S)
Hays, 2014 (control trial)	Female Sprague–Dawley rats	Left intracerebral hemorrhage	■ Paired VNS = 14 ■ Control = 12	Only RT: Bradykinesia task	Paired VNS on successful trials Extra VNS: received VNS on all trials	30 min twice daily for 5 days/ week for 6 weeks	Hit Rate at T1 and T2	■ VNS (paired + extra) vs. control: +S ■ Paired VNS vs. Extra VNS:0
Khodaparast, 2015 (control trial)	Four months old Female Sprague–Dawley Rats	Unilateral ischemic lesions of the primary motor cortex	Paired VNS = 10 Delayed VNS = 10 Control = 9	Only RT: Isometric force task training	Paired VNS to left CVN Delayed VNS: VNS every 12 s for 1 h after RT	30 min twice daily for 5 days/ week for 6 weeks	Maximal pull force, hit rate at T1 and T2	■ Paired VNS vs. control: +S ■ Paired VNS vs. delayed VNS: +S ■ Delayed VNS vs. control: 0
Hay, 2016 (control trial)	18 months old aged female fisher rats	Unilateral motor cortex ischemic lesion of M1	■ Paired VNS = 8 ■ Control = 9	Only RT: Isometric force task training	Paired VNS to left CVN delivered on successful trials	30 min twice daily for 5 days/ week for 5 weeks	Peak pull force, hit rate at T1 and T2	■ Paired VNS vs. control: +S
Meyers, 2018 (RCT)	Adult female Sprague–Dawley rats	Unilateral motor cortex ischemic lesion of M1 and dorsolateral striatum	■ Paired VNS = 9 ■ Control = 10	Only RT: supination task, isometric pull task	Paired VNS to left CVN delivered on successful trials	30 min twice daily for 5 days/ week for 5 weeks	Peak turn angle, peak pull force at T1, T2 and T3–6 weeks f/u	■ Paired VNS vs. control: +S at T2 and T3

(Continued)

TABLE 1 (Continued)

Study and study design	Animal species/ Gender	Lesion	Sample size	Control	Active intervention	Frequency and duration	Motor outcomes measures (T1 = baseline, T2: post-intervention, T3: f/u)	Results-motor outcomes
Pruitt, 2021 (control trial)	Adult female Sprague–Dawley rats	Unilateral traumatic lesion of left motor cortex	■ Paired VNS = 14 ■ Control = 14	Only RT: Isometric pull task training	Paired VNS to left CVN delivered on successful trials	30 min twice daily for 5 days/ week for 5 weeks	Maximal pull force, hit rate at and T2	■ Paired VNS vs. control: +S
Jiang, 2016 (RCT)	Male Sprague–Dawley rats	Unilateral focal ischemic lesions	■ I/R + aVNS = 8 ■ I/R = 8 ■ I/R + Sham aVNS = 8	No RT	aVNS over left cavum concha via acupuncture needles	30 min twice daily for 5 days/ week for 3 weeks	Beam-walking test and staircase test at T1 and T2	■ aVNS vs. I/R: +S ■ avNS vs. I/R+ sham: +S
Spinal cord injury								
Ganger 2018 (control trial)	Adult female Sprague Dawley rats	Right Unilateral or bilateral C6 traumatic lesion	■ Top 20% CLV = 13 ■ Bottom 20% CLV = 8 ■ Control = 9	Only RT: Isometric pull task training	Paired VNS to left CVN on successful trials during RT	F: 30 min twice daily for 5 days/ week for 5 weeks	Peak pull force at T1 and T2	■ Top 20% CLV vs. control: +S ■ Bottom 20% CLV vs. control: 0
Darrow 2020 (control trial)	Adult female Sprague Dawley rats	Bilateral contusive SCI C7/C8/ 9 wks	■ Paired VNS = 10 ■ Control = 8	Only RT: Isometric pull task training	Paired VNS to left CVN delivered when a pre-set threshold was met for pull force during RT	30 min twice daily for 5 days/ week for 5 weeks	Peak force, hit rate at T1 and T2	■ Paired VNS vs. control: +S

+S indicates a statistically significant improvement. ($p < 0.05$) in the active intervention group/VNS compared to the control group; 0 indicates no significant difference in outcomes between groups. aVNS, Auricular vagus nerve stimulation; CLV, closed loop vagus nerve stimulation; CVN, Cervical vagus nerve; f/u, follow-up; I/R, infusion and reperfusion; RT, Rehabilitation therapy; VN, Vagus nerve.

(Figure 1). Among animal studies, eight (73%) were in stroke models, one in TBI (9%), and 2 (18%) were in SCI models (Table 1). All eight human studies were conducted in people with stroke. During our literature search, there were no studies published involving VNS on motor recovery in people with SCI and TBI. We categorized our review and summarized results in the following categories: (1) VNS studies in animals with stroke models, (2) VNS studies in animals with SCI models, and (3) VNS studies in humans with stroke, further categorized in non-invasive and invasive studies.

VNS studies in animals with the stroke model

Nine studies met the eligibility criteria for our review (Table 1) (29, 31, 32, 46–51). Among these, seven studies were conducted in animal models of ischemic lesions to the motor cortex, one study (46) in animal models with unilateral intra-cerebral hemorrhage, and one study in animal models of the unilateral traumatic lesion to the left motor cortex (51). Eight of the studies (89%) implanted electrodes to stimulate the left cervical vagus nerve, and in one study (47) the left auricular vagus nerve was stimulated using acupuncture needles.

Invasive cervical vagus nerve studies

Female Sprague–Dawley Rats were used to study the effects of VNS in these studies. Prior to induced stroke or brain injury, all animals were trained to the respective rehabilitation tasks per protocol. In most studies, the intervention duration was 5 weeks; in two studies, the intervention duration was 6 weeks (Table 1). While most studies compared the effects of pairing VNS with rehabilitation compared to rehabilitation therapy, a few studies also explored the effects of delayed VNS and extra VNS (Table 1). In the paired VNS studies, the VNS group received VNS during rehabilitation therapy immediately after a successful trial at a 30 Hz frequency. In the three studies with delayed VNS group, VNS was delivered after 2 h of rehabilitation therapy every 10–12 s for 1 h (32, 46, 48). The delayed VNS protocol often optimized stimulation frequency to match the number of stimulations received by animals in paired VNS groups. The extra VNS group in two studies (29, 46) received additional VNS compared to paired VNS, delivered at a higher frequency for the same duration. The control group received identical rehabilitation therapy for the same duration as the paired VNS group without any active VNS (Table 1). Most studies performed follow-up assessments a week after the completion of the intervention. In all eight studies, paired VNS was delivered at a current intensity of 0.8 mA with 100 μs phase duration.

Across all eight studies, measured motor outcomes improved significantly in the paired VNS group compared to the control group. Extra VNS resulted in improvement in motor outcomes compared to

TABLE 2 Human stroke VNS studies demographics and baseline.

Study and study design	Population	Age in years, mean (SD)	Sample size, % male (M)	Time since stroke in months, mean (SD) or Median (IQR)	Interventions in respective groups (I, intervention; L, location of VNS; T, timing of VNS; F, frequency; CI, current Intensity)	Duration (D) and follow-up (f/u) (T1, baseline; T2, post-intervention; T3, follow-up)	Outcomes
Non-invasive VNS studies							
Capone et al. 2017/RCT	Chronic Ischemic or hemorrhagic stroke	I: 54 (5.9)	I: 7 (M: 57%)	I: 94 (39)	I: tVNS + UE robotic therapy to the affected limb	D: 10 days	Motor
					L & T: Left inner side of the tragus, before robotic therapy, every 5 min for 1 h		FMA-UE: +S
					F & CI: 30 Hz and CI range 2–4.5 mA	F: >300 point-to-point movements per session	Adverse events: No adverse events occurred, no change in BP and HR
		C: 56 (7.1)	C: 5 (M:43%)	C: 46.0 (22)	C: sham tVNS + Robotic therapy	OA: T1 and T2	
Redgrave et al. 2018/Pre-post study	Chronic ischemic stroke	65 (6.9)	13 (M:77%)	14 (IQR: 8–43)	I: tVNS + UE rehabilitation therapy to the affected limb	D: 1 h RT with sham or active tVNS, three times per week for 6 weeks	Motor
							FMA-UE: Improved pre-post[#]
					L & T: Left concha, paired with RT	F: >300 repetitions per hour session	ARAT: Improved pre-post[#]
					F & CI: 25 Hz and median (IQR) CI 1.4 (1–3.2) mA	OA: T1 and T2	Adverse events: Two reported fatigue, one lightheadedness, no change in ECG.
Wu et al. 2020/ RCT	Sub-acute Ischemic stroke	I: 65 (9.9)	I: 5 (M:50%)	I: 1.2 (0.31)	I: taVNS pre-RT followed by RT	D: 30 min sham or taVNS +30 min RT daily for 15 days	Motor
							FMA-UE: +S at T2 and T3
							WMFT: +S at T2 and T3
					L & T: Left cymba concha, pre-RT	F: multiple movements were targeted until fatigue	FIM: +S at T2 and T3
					F & CI: 20 Hz and mean (SD) CI 1.7 (0.4) mA	OA: T1 and T2, T3–12 weeks from 1st intervention	
		C: 62 (11)	C: 8 (M:73%)	C: 1.2 (0.22)	C: Sham taVNS + RT		Adverse events: One episode of skin redness, no group differences for HR & BP.

(Continued)

TABLE 2 (Continued)

Study and study design	Population	Age in years, mean (SD)	Sample size, % male (M)	Time since stroke in months, mean (SD) or Median (IQR)	Interventions in respective groups (I, intervention; L, location of VNS; T, timing of VNS; F, frequency; CI, current Intensity)	Duration (D) and follow-up (f/u) (T1, baseline; T2, post-intervention; T3, follow-up)	Outcomes
Chang et al. 2021/RCT	Chronic ischemic or hemorrhagic stroke	I: 56	I: 18 (M:50%)	26 (4.7)	I: taVNS + UE robotic therapy	D: 1 h/session	Motor
					L & T: Left cymba concha paired with robotic therapy	F: 3 ×/week for 3 weeks	FMA-UE: 0 at T2 and T3
							WMFT: 0 at T2 and T3
							MRC: 0 at T2 and T3
							MTS: 0 at T2 and +S at T3
				Only cumulative data is available	F & CI: 30 hz, 0.1–5 mA	OA: T1, T2 and T3:3 months f/u	*Both groups improved pre-post but no statistical difference was seen between groups except for MTS at f/u.
		C: 62	C:15 (M:50%)		C: Sham taVNS + UE robotic therapy		Adverse events: No serious adverse events were reported in this study.
Li et al. 2022/ RCT	Acute ischemic or hemorrhagic stroke	I: 69(12)	I: 30 (M: 50%)	I: 0.36 (0.25)	I: tavNS + RT	D: 20 min sham or active taVNS +30 min RT/session	Motor
					L & T: Left concha, pre-RT for 20 min	F: 5×/week for 4 weeks	FMA-UE, FMA-LE, FMA-S: +S at T2 and all f/u assessments
				C: 0.34(0.23)	F & CI: 20 Hz, mean (sd): 1.7(0.5) mA	OA: T1, T2, T3:3,6 and 12 months from baseline	WMFT: +S at T2 and all f/u assessments
		C: 68(12)	C:30 (M:47%)		C: Sham taVNS + RT		Adverse events: No changes in HR SBP and DBP pre-post therapy in each group. No adverse events.
Invasive VNS studies							
Dawson et al. 2016/RCT	Ischemic stroke	I:58 (17)	I: 9 (M: 78%)	I:14 (12)	I: active VNS + RT	D: 2 h per session	Motor:
							FMA-UE: +S (per protocol analysis)
							FMA-UE: 0 (intent to treat analysis)

(Continued)

TABLE 2 (Continued)

Study and study design	Population	Age in years, mean (SD)	Sample size, % male (M)	Time since stroke in months, mean (SD) or Median (IQR)	Interventions in respective groups (I, intervention; L, location of VNS; T, timing of VNS; F, frequency; CI, current Intensity)	Duration (D) and follow-up (f/u) (T1, baseline; T2, post-intervention; T3, follow-up)	Outcomes
					L & T: Left cervical vagus nerve paired stim for 2 h	F: 3 ×/week for 6 weeks	ARAT, grip strength, NHP, BBT: 0 (per protocol analysis)
							Adverse events in VNS (n):
							Surgical complication:
							Vocal cord palsy and dysphagia (1),
					F & CI: 30 Hz, 0.8 mA	OA: T1 and T2	Taste disturbance (1),
		C:61(11)	C:11 (M:82%)	C:20 (16)	C: RT only		*Stimulation-related events:*
							Hoarseness of voice or neck tingling (6),
							Nausea after a single session (1)
							Difficulty swallowing after one VNS session (1)
Kimberley et al. 2018/ RCT	Ischemic stroke	I: 60 (7)	I:8 (M:50%)	I: 18	I: active VNS + RT + home exercise	In clinic therapy:	Motor:
							FMA-UE, BBT, NHPT: 0 at T2 and T3
							WMFT: 0 at PI; +S at T3
							Adverse events in VNS:
						D: 2 h per session in clinic therapy	*Surgical complication:*
					L & T: Left cervical vagus nerve paired stim for 2 h	F: 3 x/week for 6 weeks	Surgical site infection (1)
				*SD unknown	F & CI: 30 Hz, 0.8 mA	Home Exercise:	Post-surgical SOB and dysphagia (1)
		C: 60 (14)	C:9 (M:56%)	C: 18	C: Sham VNS + RT only + home exercise	30 min daily for 90 days	Hoarseness of voice due to vocal cord palsy (1)
				*SD unknown		OA: T1, T2, and T3: 90 days f/u	*No serious adverse events associated with VNS were reported.

(Continued)

TABLE 2 (Continued)

Study and study design	Population	Age in years, mean (SD)	Sample size, % male (M)	Time since stroke in months, mean (SD) or Median (IQR)	Interventions in respective groups (I, intervention; L, location of VNS; T, timing of VNS; F, frequency; CI, current Intensity)	Duration (D) and follow-up (f/u) (T1, baseline; T2, post-intervention; T3, follow-up)	Outcomes
Dawson et al. 2021/RCT	Ischemic stroke	I: 59 (10)	I: 53 (M:64%)	I: 37 (28)	I: active VNS + RT + home exercise	In-clinic therapy:	Motor:
							FMA-UE: +S at T1 and T2
							WMFT: +S at PI; +S at T1 and T2
							Serious adverse events in VNS:
						D: Avg 90 min/session in clinic therapy	*Surgical complications:*
						F: 3 ×/week for 6 weeks	Surgical site pain, *n* = 24(22%)
					L & T: Left cervical vagus nerve paired stim for 2 h	Home Exercise:	Hoarseness of voice, *n* = 9 (8%)
					F & CI: 30 Hz, 0.8 mA	30 min daily for 90 days	Vocal cord palsy, *n* = 1 (0.01%)
		C: 61 (9)	C:55 (M:65%)	C:40 (31)	C: Sham VNS + RT only + home exercise	OA: T1, T2 and T3: 90 days f/u	*No serious adverse events associated with the device stimulation were reported.

+S indicates a statistically significant improvement ($p < 0.05$) in the active intervention/VNS group compared to the control group; 0 indicates no significant difference between groups, [#]Statistical analysis was not performed. FMA-LE, Fugl-Meyer Assessment—lower extremity; FMA-S, Fugl-Meyer Assessment –sensory; MAL, Motor activity log; MRC, Medical Research Council Motor Power Scale; MTS, Modified Tardieu Scale; NHPT,: Nine Hole Peg Test; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; RT, Rehabilitation therapy; OA, Outcome assessment.

control which was statistically significant but did not result in any additional benefit compared to paired VNS. However, in studies with delayed VNS groups, results were inconsistent. In two studies (32, 48), there were no differences in outcomes between delayed VNS and controls; in one study (29), the delayed VNS group had better motor outcomes than the control, but the paired VNS group had statistically significantly improved motor outcomes compared to the extra VNS and delayed VNS group. There was no difference in lesion size pre and post-intervention based on histological processing in all eight studies. None of the above studies reported or recorded any adverse events during the study procedures.

Auricular vagus nerve study in stroke

In this study, male Sprague–Dawley rats with unilateral focal ischemic lesions of the motor cortex, were randomized into three groups (47). One group received only reperfusion therapy, a second group received both reperfusion therapy and stimulation of the auricular branch of the vagus nerve over the left cavum concha with acupuncture needles, and a third group received reperfusion therapy, with acupuncture needles implanted, but VNS stimulation was not delivered. In the second group, VNS was delivered at 0.5 mA current intensity at 20 Hz every 5 mins for 1 h. None of the groups received rehabilitation therapy. Functional recovery was measured by the beam-walking test and staircase test. At 1 week follow up, these tests revealed a statistically significant improvement in neurological function in the active VNS group with reperfusion compared to the other two groups, which persisted at the third week. Additionally, the size or volume of the infarct significantly reduced in the active VNS group compared to the other two groups.

VNS studies in animals with SCI model

Only two studies in animal models of SCI met the eligibility criteria for our review (25, 52). Both studies were performed in female Sprague–Dawley rats, and in both studies animals sustained traumatic lesions at the cervical level (Table 1). Electrodes were directly implanted on the left cervical vagus nerve for stimulation. Similar to stroke studies, animals were trained before traumatic cervical SCI. The intervention duration was 5 weeks, and stimulation duration and

parameters were identical to stroke animal studies at a current intensity of 0.8 mA, frequency of 30 Hz, and 100 μs phase duration (Table 1). In both studies, rats received isometric pull task training paired with or without VNS (control). Outcomes were measured 1 week after completion of the intervention.

In one study (52), animals were divided into three groups: (a) a control group received rehabilitation without VNS, (b) the top 20% closed loop VNS (CLV) group in which VNS was delivered immediately after an isometric pull task trial when pull force was within the top 20% of prior trials and (c) the bottom 20% CLV group in which VNS was delivered in which pull forces fell within the bottom 20% of the prior trials resulting in a significant time gap between VNS and successful trials. In this study, the top 20% of the CLV group had improvement in peak pull force post-intervention compared to the control group, which was statistically significant, but the bottom 20% of the CLV group and control group had no difference in peak pull force compared to controls. In the second study, pairing VNS with rehabilitation resulted in a statistically significant improvement in forelimb strength measured by peak pull force and hit rate compared to the control group (25). Adverse events were not documented in either study.

VNS studies in humans with stroke

Among eight human studies, five (63%) utilized a non-invasive mode of VNS, and three (37%) studies involved surgical implantation of electrodes on the cervical portion of the vagus nerve to deliver VNS.

Among the seven RCTs included in the quantitative evaluation (Table 3) of outcomes, 3 (43%) were found to have low risk, 4 (57%) some risk of bias (Supplementary material 1), and 0 (0%) high risk of bias.

Non-invasive VNS human stroke studies

Among five non-invasive studies, three studies (53–55) included patients with chronic stroke (occurring 6 months prior), one study (56) was done in sub-acute stroke (>1 month and <3 months since stroke), and one study (57) in acute stroke patients (stroke onset < 1 month). Four of the five studies were randomized, blinded RCTs receiving active transcutaneous auricular VNS (taVNS) or sham VNS. The fifth study was a single group examining the effects of taVNS pre and post-intervention. In all studies, the left auricular branch of the vagus nerve was stimulated transcutaneously with surface electrodes. However, specific placement varied slightly between studies (Table 2). In two studies, taVNS was paired with rehabilitation therapy, each lasting up to 1 h. In the other three studies, taVNS was delivered before rehabilitation therapy, ranging from 20 min to 60 min. Stimulation frequency ranged from 20 to 30 Hz, with 20 Hz being the most common frequency used. The stimulation intensity was individually adjusted according to each participant's tolerability (Table 2), and current intensities ranged from 0.1 to 5 mA. In all four RCTs, the control group received sham taVNS with the same duration and frequency of rehabilitation therapy as the active intervention group. In two studies, upper extremity robotic therapy was delivered, and in three studies, conventional rehabilitation therapy was delivered; all studies focused on multiple repetitions of upper extremity movements. Study duration, total number of sessions, and frequency ranged from 10 days to 6 weeks and 10–20 sessions, respectively (Table 2). The Fugl-Meyer upper extremity assessment (FMA-UE) was the primary motor outcome for all studies. Few studies measured additional motor outcomes such as the wolf motor function test (WMFT), action recovery arm test (ARAT), functional independence measure (FIM), Medical Research Council motor power scale, and the modified Tardieu scale (Table 2).

Outcomes

Four out of five studies reported improvement in FMA-U compared to control or baseline. The median (IQR) for mean change in UE-FMA scores from baseline to post-intervention in the VNS group ($n = 60$) was 6.2 (4.8–8.4), and in the control group ($n = 58$) was 3 (2.9–3.5). The relative improvement of FMA scores in three RCTs ranged from 8% to 27% (Figure 2) at post-intervention assessment, and these improvements were boosted at follow–up in two studies (Figure 2) (53, 56, 57). There were no serious adverse events reported in any of the studies. Most of the studies monitored changes in blood pressure and heart rate; no significant changes were noted in these measures.

TABLE 3 Results-mean improvement in upper extremity Fugl-Meyer scores in people with stroke.

	VNS group, mean (SD)	Control group, mean (SD)	Mean improvement in FMA-UE scores (CI)	*p*-value	Risk of bias
Non-invasive VNS studies					
Capone et al. 2017/RCT	5.4 (7.2)	2.8 (7.1)	2.6*	0.048	Some
Wu et al. 2020/RCT	6.9 (1.9)	3.2 (1.2)	3.7 (2.3 to 5.1)	≤0.001	Low
Chang et al. 2021/RCT	3 (0.57)	2.9 (0.5)	0.14*	≥0.23	Some
Li et al. 2022/RCT	13*	4.7*	8.3*	<0.05	Some
Invasive VNS studies					
Dawson et al. 2016/RCT	8.7 (5.8)	3 (6.1)	5.7 (−0.36 to 12)	0.064 (ITT)	Some
	9.6 (5.3)	3 (6.1)	6.5 (0.42 to 12.6)	0.038 (PP)	
Kimberley et al. 2018/ RCT	7.6*	5.3*	2.3 (−1.9 to 6.5)	0.26 (ITT)	Low
Dawson et al. 2021/RCT	5 (4.4)	2.4 (3.8)	2.6 (1 to 4.2)	0.0014	Low

*SD was not provided in the original paper. CI, Confidence interval; ITT, Intention to treat analysis; PP, Per protocol analysis.

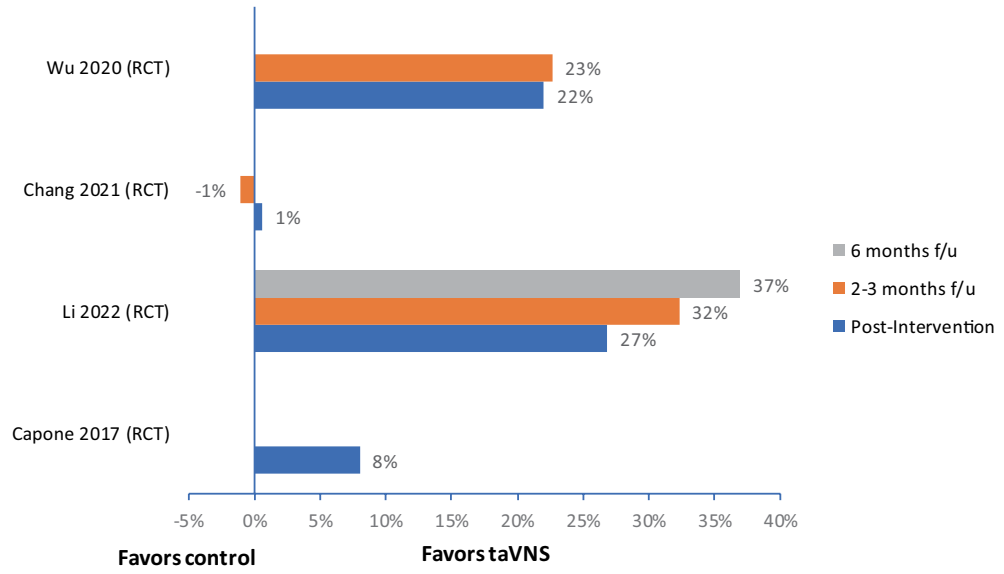

FIGURE 2
Relative change in FMA-UE with taVNS in people with stoke. f/u, follow-up.

Invasive VNS human stroke studies

Two pilot studies and one pivotal Phase III study using invasive VNS for stroke rehabilitation met our enrollment criteria (27, 28, 33). Only the pivotal trial was powered for efficacy. In total, 146 participants were enrolled. All participants were diagnosed with ischemic stroke between 4 months and 10 years after stroke onset and demonstrated moderate to severe impairment based on FMA-UE or ARAT. In total, 142 (97%) participants completed all treatment sessions. All three studies used Vivistim® Paired VNS System™ as an implant device. The implant surgery was performed under general anesthesia on the left vagus nerve. An overview of the stimulation parameters is given in Table 2. Specific VNS parameters in all three studies were the same using 0.5 s burst VNS (0.8 mA, pulse duration 100 μs, frequency of 30 Hz). While one pilot study used VNS implants only in the active VNS+ rehabilitation group, in the other two studies, VNS was implanted in all participants, including controls. Thus, 134 participants had VNS implantation in these three studies. In-clinic rehabilitation therapy was provided three times per week for 6 weeks (total of 18 sessions) paired with VNS in the active intervention group. Participants in the control group received similar upper limb rehabilitation in all studies, and in two studies, it was combined with sham VNS (Table 2). In the active intervention group, the average number of stimulations during each session ranged between 414 and 444. The two-hour therapy session consisted of stretching and individualized progressive functional tasks targeting movements required to perform activities of daily living such as reach and grasp, etc. Each task was performed for about 10 min, averaging 450 movements per session. After 6 weeks of in-clinic therapy in two studies, participants continued with a 30-min home exercise program over 3 months (27, 33). The primary safety outcome measure was the number of serious adverse events related to the device implantation or rehabilitation therapy with or without VNS.

Outcomes

In all three studies, the primary efficacy outcome measure was a change in FMA-UE from baseline to the first day after the completion of in-clinic therapy, and the safety outcome measure was the number of serious adverse events related to the device implantation or rehabilitation therapy with or without VNS. Details on improvement in FMA-UE scores in VNS and control groups are reported in Table 3. Overall median (IQR) improvement in FMA-UE scores in the VNS group ($n = 70$) was 7.6 (6.3–8.2), and in the control group ($n = 75$) was 3 (2.7–4.2). These improvements were not statistically significant in these two studies. However, in these two studies, 67 and 88% of participants achieved a clinically meaningful response on the FMA-UE score in the VNS group compared with controls, in which 36 and 33%, respectively, achieved a clinically meaningful improvement. In the third RCT by Dawson et al., clinically meaningful improvement in FMA-UE was achieved in 23 (47%) participants in the VNS group vs. 13 (24%) participants in the control group ($p = 0.0098$). The relative improvement in FMA-UE in these three studies ranged from 3% to 13% in the active VNS group compared to controls, and this improvement was further accentuated at 90 days follow-up in studies that had a home exercising program (Figure 3).

Adverse events

The majority of the serious adverse events were post-surgical and related to device implantation. Among 134 participants who had VNS implantation in these three studies, three developed vocal cord palsy (2%), two developed dysphagia (1.4%), one participant had surgical site infection (0.7%), one reported disturbance in taste (0.7%), and 10 participants reported hoarseness of voice (7%) (27, 28, 33). Authors reported all the events were resolved at follow-up. Vocal cord palsy took the longest to resolve, with up to 9 months of recovery in one study (28). There were no serious adverse events with the vagus nerve stimulation protocol. The most commonly reported VNS-related adverse effects were occasional tingling and hoarseness in some participants, which did not persist once the stimulation was aborted.

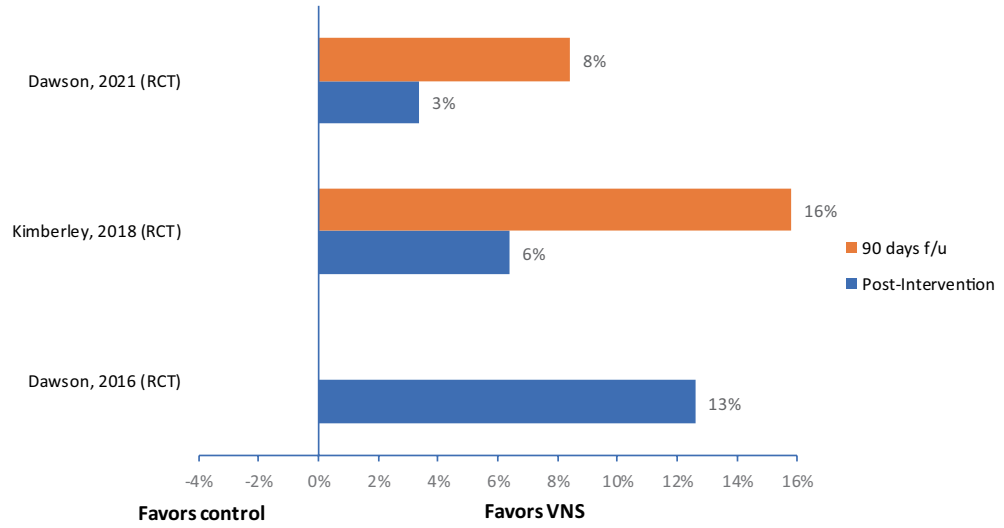

FIGURE 3
Relative change in FMA-UE with CVNS in people with stoke. f/u, follow-up.

Invasive and non-invasive VNS human SCI studies

There are no published human invasive and non-invasive studies of VNS on motor recovery in SCI. However, we are aware of two centers studying the effects of paired invasive VNS with rehabilitation on motor recovery in people with SCI (NCT05601661, NCT04288245). Results from these studies will provide data on the safety, feasibility, and efficacy of paired VNS on motor recovery in people with SCI.

Discussion

We aimed to comprehensively review animal and human VNS studies on motor recovery in stroke, TBI, and SCI models/populations. Overall, in 11 studies with rat models of stroke or SCI, upper extremity motor function outcomes consistently improved across both invasive and non-invasive VNS treatment. Notably, all studies demonstrated relatively identical VNS parameters (amplitude, frequency, and duration of stimulus) and intervention duration and frequency. In 10 studies, task training paired with active VNS (up to 9,000 stimulations over 5–6 weeks) improved motor outcomes compared to controls with sham VNS. In these studies, active VNS was delivered only during a successful attempt. Alternative stimulation protocols, including delayed VNS delivered after the rehabilitation therapy and extra VNS delivered at a higher frequency on all trials resulting in >9,000 stims over 5 weeks, appear to have an inconsistent and inferior degree of effect on motor outcomes in comparison to paired VNS during only successful trials. Only one animal SCI study further assessed the importance of triggering VNS on the most successful movements (52). In this study, one group received VNS groups on stronger trials (higher pull force), and another VNS group received VNS only during weaker trials. The group that received VNS during stronger trials had statistically significant improvement in peak pull force post-intervention compared to the control group, but the group that received VNS during weaker trials had no difference in peak pull force compared to controls. Improvement in motor recovery after VNS treatment in animal models was not associated with lesion size change except in one animal study. In the study by Jiang et al., auricular VNS 30 min twice daily for 3 weeks during the acute phase after reperfusion therapy resulted in a reduction in infarct size compared to controls with only reperfusion with or without sham VNS. In this acute VNS stimulation model, additional findings of improved surviving neurons, angiogenesis, and increased expression of neurotrophic and pro-angiogenic factors were present, suggesting a neuroprotection mechanism if applied during the acute phase (47). The improved motor recovery without reducing lesion size in the sub-acute phase was hypothesized secondary to enhancing plasticity in residual motor networks (25, 46, 52).

Four of the five non-invasive human studies demonstrated motor improvements compared to sham control. These improvements were present in three RCTs and compared to the baseline in one pre-and post-intervention study without controls. However, several limitations were noted in these studies, including smaller sample sizes (no power calculations), lack of temporal precision on the application of VNS during rehabilitation training, and heterogeneity of intervention type, frequency, and durations, which limits the interpretation of these study results. The human-invasive VNS studies consistently demonstrated relative motor improvements (Figure 3) but relative improvement varied in each study. Two studies assessing home programs for 90 days were promising for continuing improvements over time with continued in-home exercise programs with VNS. Indeed, in the largest trial of VNS for motor recovery in humans, the findings are promising to enhance motor outcomes compared to traditional therapies. However, the dosing and precision of VNS relative to movement or task, identified as a critical component in animal studies, have not yet been studied in humans.

Due to heterogeneity in study protocols as mentioned above and lack of power in most human studies to find the efficacy, we did not perform a meta-analysis. Instead, we provided relative improvement in outcomes in active VNS group compared to controls for individual

RCTs (Figures 2, 3). It is crucial to study the comparison of non-invasive and invasive VNS on motor recovery utilizing a standardized rehabilitation and VNS protocol for a meaningful comparison in future.

We noted no publications assessing VNS in humans with SCI, but we found two active ongoing VNS clinical trials (NCT05601661, NCT04288245) in individuals with chronic (>12 months) cervical spinal cord injury for upper extremity function. VNS studies in individuals with SCI pose additional challenges and require additional considerations. Individuals with cervical SCI often undergo surgical procedures for anterior cervical discectomy and fusion (ACDF) after the SCI, resulting in subsequent scarring in the anterior cervical area, which can complicate electrode implantation on the cervical vagus nerve. Some individuals develop sub-clinical or clinical vocal cord paralysis after ACDF, and VNS implantation surgery is also associated with the risk of vocal cord paralysis. To mitigate this risk, laryngoscopic evaluation of vocal cords is recommended before device implantation. Additionally, autonomic dysfunction in individuals with SCI results in bradycardia, autonomic dysreflexia, and orthostatic hypotension, which warrants the need for safety and feasibility studies prior to rapid translation of this intervention in individuals with SCI.

Conclusion

Based on our review, we conclude that VNS may enhance the effects of rehabilitation therapy and improve motor outcomes in human stroke populations. Some additional risks are associated with device implantation with the invasive mode of VNS. However, the risk of serious adverse events that lasted for a longer duration is ≤2%. The following studies are needed to address the current gap in the literature: (1) studies to evaluate the temporal precision of VNS with respect to task training, (2) comparative effectiveness studies to examine the effects of non-invasive and invasive VNS compared to control to determine the additional benefit at the risk of vocal cord paralysis, dysphagia, and other risks associated with device implantation in invasive VNS, (3) dosing studies to determine optimal stimulation parameters, frequency, and duration of paired VNS therapy in both clinic and home settings to optimize the outcomes, and (4) studies to assess safety, feasibility, and efficacy of both non-invasive and invasive studies in individuals with TBI and SCI.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

RK: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. AM: Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Data curation. AP: Writing – review & editing. NY: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1390217/full#supplementary-material

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The efficacy and safety of bilateral synchronous transcutaneous auricular vagus nerve stimulation for prolonged disorders of consciousness: a multicenter, double-blind, stratified, randomized controlled trial protocol

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Background: Treatment of disorders of consciousness (DOC) poses a huge challenge for clinical medicine. Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation method, which shows potential in improving recovery of DOC. However, the evidence came from single-center, small-sample randomized controlled trial, which is insufficient to form a conclusion. Thereby, we propose a prospective, multicenter, double-blind, stratified, two-arm randomized controlled trial protocol to investigate the efficacy and safety of bilateral synchronous taVNS for treatment of DOC.

Methods: We aim to recruit 382 patients with prolonged DOC, and divide them into an active stimulation group and a sham stimulation group. The patients in the active stimulation group will receive bilateral synchronous taVNS with a 200 μs pulse width, 20 Hz frequency, and personal adjusted intensity. The sham stimulation group will wear the same stimulator but without current output. Both groups will receive treatment for 30 min per session, twice per day, 6 days per week lasting for 4 weeks. The clinical assessment including Coma Recovery Scale-Revised (CRS-R), Full Outline of Unresponsiveness (FOUR), Glasgow Coma Scale (GCS), and Extended Glasgow Outcome Scale (GOS-E) will be conducted to evaluate its efficacy. Heart rate variability (HRV), blood pressure, and adverse events will be recorded to evaluate its safety.

Discussion: These results will enable us to investigate the efficacy and safety of taVNS for DOC. This protocol will provide multicenter, large-sample, high-quality Class II evidence to support bilateral synchronous taVNS for DOC, and will advance the field of treatment options for DOC.

Clinical trial registration: https://www.chictr.org.cn/showproj.html?proj=221851, ChiCTR2400081978.

KEYWORDS

transcutaneous auricular vagus nerve stimulation, coma recovery scale-revised, heart rate variability, randomized controlled trial, disorders of consciousness

Introduction

Disorders of consciousness (DOC) refer to the state in which an individual's response to external stimuli is reduced or even non-responsive. The DOC caused by diseases such as traumatic brain injury, intracerebral hemorrhage, cerebral infarction, and cardiac arrest, which are manifested as alterations in arousal and/or awareness (1), including coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), and minimally conscious state (MCS) (1, 2). Coma is defined as a state with completely lack of arousal (eyes closed) and awareness (3). While VS/UWS is defined as preserved arousal (eyes open) but without awareness (4). MCS is defined as the minimal, reproducible, but inconsistent state of awareness (5), without (MCS-) or with (MCS+) evidence of language function (6). In recent years, with the rapid development of modern medicine, the increasingly successful treatment for severe brain injury patients has led to a continuous increase in the number of patients falling into long-term survival with DOC (7). A DOC lasting up to 28 days is termed as a prolonged DOC (pDOC) (8). It poses a huge challenge for clinical medicine, as well as a huge pressure on families and society (7).

Numerous researchers and clinicians are devoting to improve the conscious state of patients and accelerate their recovery. Medications (amantadine, midazolam, intrathecal baclofen, etc.), invasive and non-invasive brain stimulation (deep brain stimulation, spinal cord stimulation, transcranial direct current stimulation, repeated transcranial magnetic stimulation, etc.), sensory stimulation (motor-based therapy, auditory-based training, music therapy, and multi-sensory training), hyperbaric oxygen and other treatments have been used to achieve better rehabilitation goals (9). The evidence-based basis for these treatments has been continuously improved in recent years (10, 11). Vagus nerve stimulation (VNS) is a type of brain stimulation technique, which has been considered as one of the latest neuromodulation methods benefit to patients with DOC.

The first clinical application of VNS was the treatment for intractable partial seizures (12). Its clinical application was approved by the Food and Drug Administration (FDA) in 1997 (13). Currently, besides intractable partial seizures, the FDA has approved VNS for medication-resistant depression (14), episodic cluster headaches (15) and moderate-to-severe upper extremity motor impairments following chronic ischemic stroke (16).

According to the International Consensus Based Review and Recommendations for Minimum Reporting Standards in Research on Transitional VNS (Version 2020) (17), there are four currently accepted VNS methods: cervically implanted VNS (iVNS), transcutaneous cervical VNS (tcVNS), transcutaneous auricular VNS (taVNS), and percutaneous auricular VNS (paVNS). Among them, taVNS is a safe, non-invasive, and easy-to-use treatment option, compared to iVNS (18). The first use of VNS for DOC was published in 2017 with a case report (19). A VS/UWS due to cardiac arrest developed to MCS after 4 weeks of taVNS. In the same year, another case report also reported that a patient with VS/MCS developed to MCS after 4 weeks of iVNS (20). Subsequently, 5 (21), 10 (22), and 14 (23) patients with DOC were treated with VNS in 3 case series (1 iVNS and 2 taVNS). These case series indicated that VNS improved the behavioral responses (conscious state) of patients and was safe and feasible for DOC.

However, these uncontrolled case reports (19, 20) and case series (21–23) only provided weak Class IV and Class V evidence of treatment efficacy. It cannot be ruled out that the impacts are from spontaneous recovery, especially considering the acute to subacute background of the enrolled patients. Recently, we provided the highest level of evidence for the efficacy and safety of VNS for DOC with a single-center double-blind randomized controlled trial (RCT) (28 active versus 29 sham stimulation) (24). It indicated that 4 weeks' taVNS significantly improved the Coma Recovery Scale-Revised (CRS-R) score of MCS patients, and without significant side effects. In order to further confirm and validate the efficacy and safety of taVNS, as well as to provide more comprehensive and reliable evidence, we propose here a multicenter, double-blind, stratified, two-arm RCT.

Methods and analysis

Study design

This is a prospective, multicenter, double-blind, stratified, two-arm RCT. This study protocol is designed according to the Declaration of Helsinki. It has been approved by the Ethics Committee of the Affiliated Rehabilitation Hospital of Nanchang University (SFYYXLL-PJ-2023-KY015) and has been registered at the Chinese Clinical Trial Registry (ChiCTR2400081978, https://www.chictr.org.cn/showproj.html?proj=221851). As the participants are patients with DOC, informed consent will be obtained from their legal representatives. The study design and final report will follow the Consolidated Standards of Reporting Trials (CONSORT) statement and its extension to non-pharmacologic treatment interventions. Figure 1 shows the study flowchart.

Population

The study participants are patients with pDOC who will be recruited from 8 large and experienced centers of rehabilitation medicine: (1) Affiliated Rehabilitation Hospital of Nanchang University; (2) the First Affiliated Hospital of Nanchang University; (3) Ganzhou People's Hospital; (4) the First Affiliated Hospital of Gannan Medical College; (5) Fuzhou First People's Hospital; (6) Xinyu People's Hospital; (7) Jiujiang First People's Hospital; (8) Nanchang Hongdu Hospital of Traditional Chinese Medicine. Patients will be screened by trained medical personnel based on the inclusion and exclusion criteria.

Inclusion criteria: (1) Aged 18 to 65 years old; (2) Acquired brain injury patients with clear etiology; (3) Diagnosed as VS/UWS or MCS (based on 5 consecutive days of CRS-R evaluation, performed by two individuals, and consulted with a third party in case of dispute); (4) Fall in DOC up to 28 days; (5) The skin at the site of stimulation is intact; (6) Sign informed consent.

Exclusion criteria: (1) Patients whose vital signs are unstable; (2) Patients with active intracranial hypertension; (3) Patients with pacemakers, cochlear implants, or metal implants in the brain; (4)

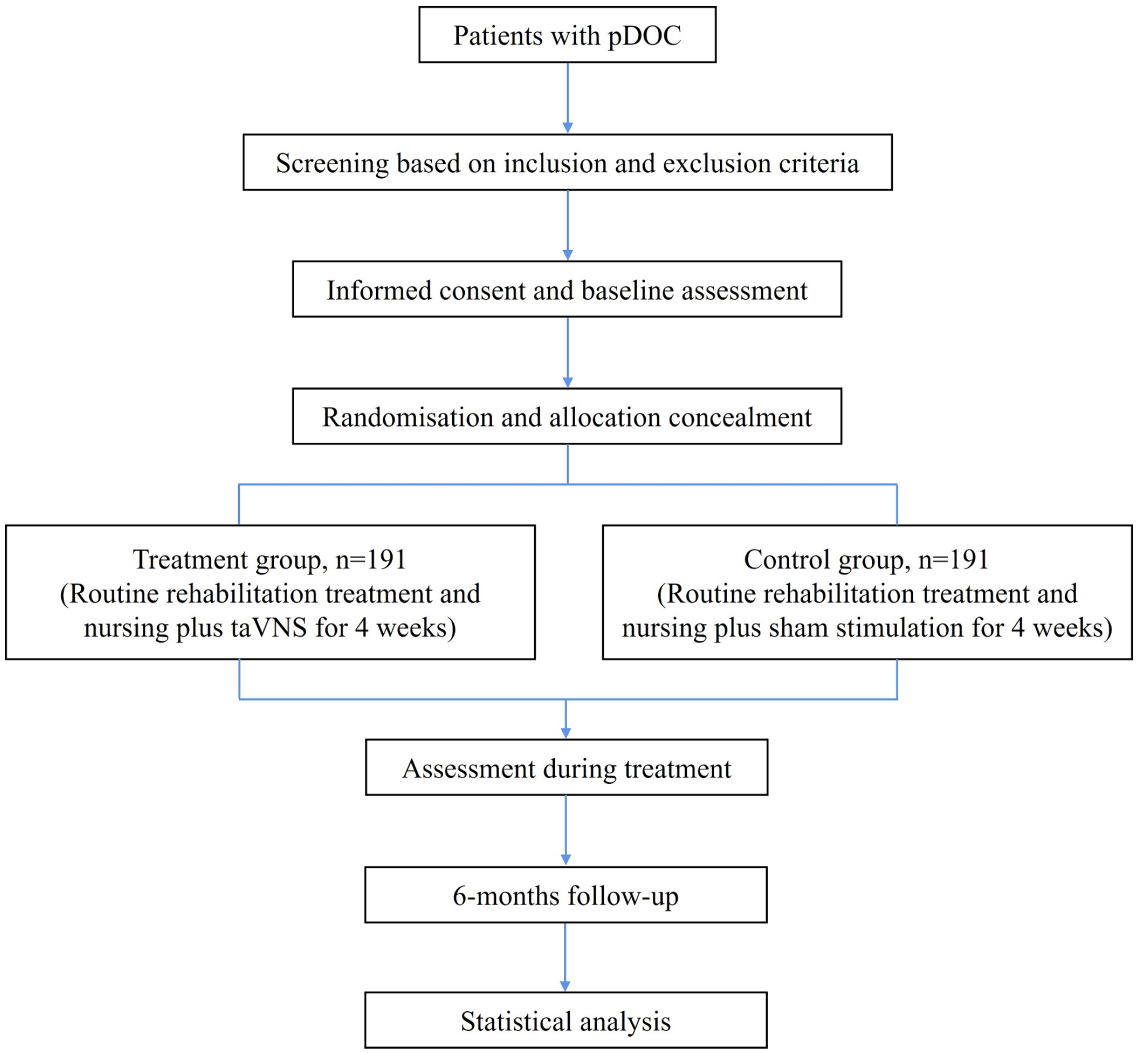

FIGURE 1
Study flowchart. pDOC, prolonged disorders of consciousness.

Patients with a history of cerebral nervous system disease prior to brain injury; (5) Patients with deep sedation caused by general anesthesia (e.g., propofol) or central sedatives (e.g., benzodiazepines, opioids); (6) Patients with bradycardia, atrial fibrillation, or atrioventricular block; (7) Pregnant patients.

Withdrawal criteria: (1) Recurrent seizures are difficult to control during treatment; (2) Life-threatening diseases (such as severe intracranial infections and cerebral hernia) occur; (3) Patients who consistently exhibit signs of pain below the threshold of given stimulus intensity; (4) Proactively exit.

Sample size

The required sample size was calculated based on the results of our previous single-center RCT (24). In which, the difference of total CRS-R score between the taVNS group and the sham stimulation group after treatment was 10.93 ± 4.99 vs. 9.28 ± 4.38. We set the test power (1-β) to be 90%, the type I error rate (α) to be 0.05, and the group allocation of the two groups to be equal. The calculated sample size was $N1 = N2 = 172$. Considering that 10% of patients will be lost during follow-up, a total of 382 patients with pDOC will eventually be enrolled.

Randomization and allocation concealment

The grouping scheme adopts stratified block randomization. Specifically, patients are first stratified according to the research center and then stratified according to the degree of DOC (VS/UWS or MCS). Then, patients are randomized 1:1 in variable block sizes, with stratification balancing by research center and degree of DOC. The randomization procedure is performed by independent statistical experts who are not involved in the study's implementation or statistics. The study secretary places the generated random numbers and the grouping outcomes separately into opaque envelopes and sends them to each participating sub-center. After patients are confirmed to be enrolled, the sub-center doctors sequentially open the numbered envelopes to complete the grouping.

Intervention protocol

After grouping, both groups will undergo identical routine rehabilitation therapy and nursing. The active stimulation group will receive bilateral synchronized taVNS treatment (JY-VNS-200, Jingyi Medical Technology Co., Ltd., Jiangxi, China, Figure 2A). Electrotherapy is performed through a pair of metal electrodes, which are placed on the headphone-like stimulating end. The metal electrodes correspond directly to the cymba conchae and the cavum conchae (Figure 2B). Before treatment, the stimulation sites are thoroughly cleansed with alcohol to minimize impedance and ensure optimal conductivity. Treatment parameters: sine wave, 200 μs pulse width, 20 Hz frequency, 2 mA initial current intensity, 30 s on/30 s off cycle. The stimulation intensity will be gradually adjusted downwards in steps of 0.5 mA based on the patient's tolerance (pain perception). To accurately distinguish pain from non-pain, the Nociception Coma Scale-Revised (NCS-R) will be utilized both initially and throughout the stimulation process, with a threshold of 4 points (25, 26). If the NCS-R score indicates pain (i.e., a score of ≥4), the stimulation intensity will be promptly reduced by 0.5 mA, and the NCS-R evaluation will be repeated. Patients who continue to exhibit signs of pain below the 0.5 mA threshold will be excluded from the study. To guarantee optimal contact between the electrodes and the ear skin, as well as to minimize the risk of electric burns, the device incorporates both an alarm function and a protection mechanism. These safety features will be activated whenever the electrodes fail to maintain adequate contact with the ear skin, such as when impedance exceeds 10 KΩ or the single pulse energy surpasses 8 mJ.

The device is presented with Mode A and Mode B. One is active stimulation, and the other is sham stimulation with no current output. Both modes exhibit identical screen displays and button operations (the current intensity can be adjusted, while other parameters are fixed to the values mentioned above). This makes researchers and device operators unaware of which stimulation is the active one. The two groups will receive treatment for 30 min per session, twice a day, 6 days a week for 4 weeks. The above treatment parameters and time refer to our previous single-center study (24) and peer studies (19, 23, 25). Bilateral synchronous taVNS will be performed at the same time before the start of the routine rehabilitation therapy in the morning and afternoon every day, under the operator's continuous monitoring.

Blinding and unblinding

The study is a double-blind design. The A/B Mode of the device effectively blinds the researchers. The participants are patients with pDOC who remain unaware of the study's specifics. Furthermore, the evaluators and data analysts are kept blind to the grouping of patients. After the trial, the person in charge of blinding who did not participate in the study will break the blinding. When patients experience serious complications (such as cardiac arrest) during the trial and they are suspected to be related to taVNS, the sub-center can call the person in charge of blinding for emergency unblinding.

Data collection

After enrollment, demographics and baseline data of patients in both groups will be collected, including gender, age, cause of injury, duration of DOC, CT results (subarachnoid hemorrhage, hydrocephalus), pupillary light reflex (none, one side, both sides), cranial surgery (with or without), tracheotomy (with or without), multiple injuries (with or without), initial CRS-R, Full Outline of Unresponsiveness (FOUR), and Glasgow Coma Scale (GCS) scores.

Patients in both groups will be evaluated via CRS-R, FOUR, and GCS scores after 2 weeks of treatment and at the end of treatment (after 4 weeks of treatment). The improvement in the CRS-R scores at the end of treatment is the primary outcome. Extended Glasgow Outcome Scale (GOS-E) scores will be followed up at 3 and 6 months after the end of treatment. During follow-up, if the patients are still in the hospital, they will be evaluated in the ward. If the patients are discharged, they will be evaluated via structured phone interviews with themselves, their family members, or caregivers. According to reports, the assessment of GOS-E via phone is a valid alternative to

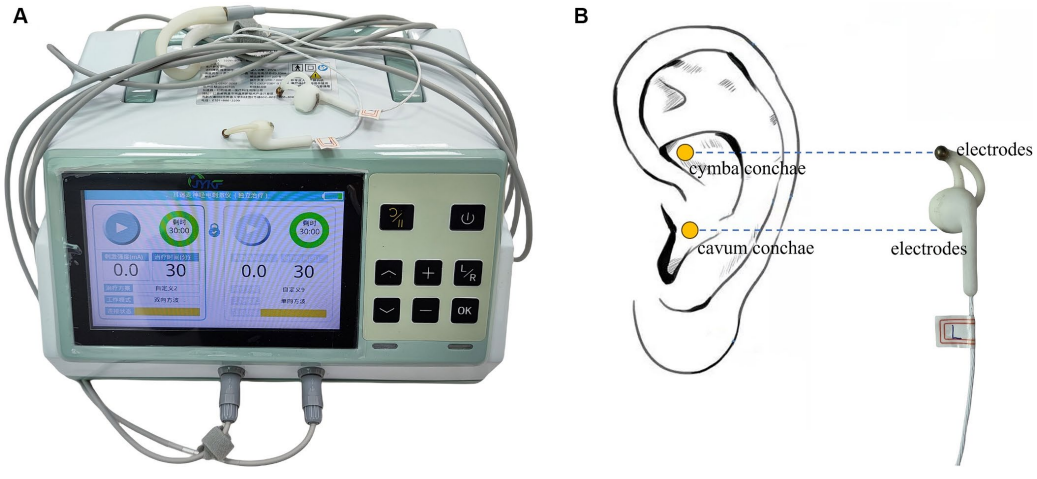

FIGURE 2
(A) Bilateral synchronous taVNS device; **(B)** stimulation sites and electrodes.

face-to-face interviews when face-to-face contact is not possible. The level of agreement (Cohen's weighted κ) between the two is good (27). The evaluation process during treatment and follow-up is shown in Figure 3. The total length of hospital stay and mortality during treatment and follow-up will also be recorded.

The cardiovascular system is doubly innervated by the sympathetic and parasympathetic nerves. The vagus nerve is a mixed cranial nerve that contains parasympathetic nerve fibers. In theory, stimulating the vagus nerve may increase the risk of its mediated bradycardia and hypotension. Heart rate variability (HRV) analysis can provide information on the balance between the sympathetic and parasympathetic pathways (28). It is a useful tool for evaluating cardiac autonomic regulation (28). Therefore, we will use a heart rate chest strap (Maijin Intelligent Technology Co., Ltd., Qingdao, China) and the Elite HRV smartphone application (Elite HRV Inc., Asheville, NC, United States) to collect and analyze patients' HRV information. Specifically, placing the sensor of the chest strap at the level of the heart in front of the chest. Adjusting the length of the elastic strap to ensure close contact between the electrode area and the skin. Connecting the chest strap to the Elite HRV application on the phone via Bluetooth. We will collect and analyze HRV information of the patients for 30 min before and during the first taVNS, including mean heart rate, mean RR, the standard deviation of normal-to-normal RR intervals (SDNN), the root mean square of successive differences (RMSSD), the proportion of NN50 divided by the total number of normal-to-normal RR intervals (PNN50), low-frequency (LF) power, high-frequency (HF) power, total power, and LF/HF ratio. The chest strap records the cardiac electrical activity and extracts heart rate data from the electrocardiogram (ECG) waveforms, which has detection results comparable to Holter ECG (29–31). For blood pressure, we will record it once separately before and during the patient's first taVNS. In addition to our recordings, ECG monitoring will also be performed on patients during each stimulation to detect vital signs.

Poor skin and electrode contact may lead to skin burns. Although the device provides burn risk alarm and protection mechanisms, we will still record skin burns at the stimulation sites, including exudation, blisters, and other skin damage. We will record any adverse events that may occur in various systems during the trial period, which may affect the patient's prognosis. These include epilepsy, paroxysmal sympathetic hyperactivity, hydrocephalus, intracranial infection (nervous system); deep vein thrombosis, pulmonary embolism, cardiac arrest (cardiovascular system); pulmonary infection, acute respiratory distress syndrome (respiratory system); gastric bleeding (digestive system); and urinary tract infection (urinary system). These adverse events are largely unrelated to taVNS. In addition, we will collect records on the type and volume of routine rehabilitation therapy for both groups during the trial period.

Data management

The data collected from each patient will be recorded in a standardized case report form (CRF), and the CRF will be transmitted to the coordinating center (Affiliated Rehabilitation Hospital of Nanchang University) after the trial is completed. The researchers responsible for data management at the center will store these data anonymously on the Research Electronic Data Capture platform. Only researchers responsible for data management can access its content. After all data are stored, the database will be locked and sent to the research statistician for analysis according to the predetermined statistical analysis plan.

Statistical analysis

Statistical analysis will be performed using R software. For demographic and baseline data, the quantitative data that conform to a normal distribution will be expressed as mean ± standard deviation ($\bar{x} \pm s$) and differences between groups will be analyzed using the independent samples *t*-test. The quantitative data that do not conform to a normal distribution will be expressed as median (interquartile range, IQR) and differences between groups will be analyzed using the Mann–Whitney U test. The qualitative data will be analyzed using the chi-square test or Fisher's exact test. For the efficacy indicators, in order to detect changes in CRS-R, FOUR and GCS scores over time and differences between groups, a linear mixed-effects model (LMM) with repeated-measures analysis from the "nlme" package in R software will be used. *Post-hoc* exploratory subgroup analyses will explore the effects of taVNS on subgroups according to different levels of consciousness and different etiologies. For safety indicators, HRV and blood pressure data were tested for normal distribution and analyzed using the paired-samples *t*-test or Wilcoxon Signed-rank test. Differences between groups in the incidence of adverse events were analyzed using the chi-square test or Fisher's exact test. $p < 0.05$ was considered statistically significant.

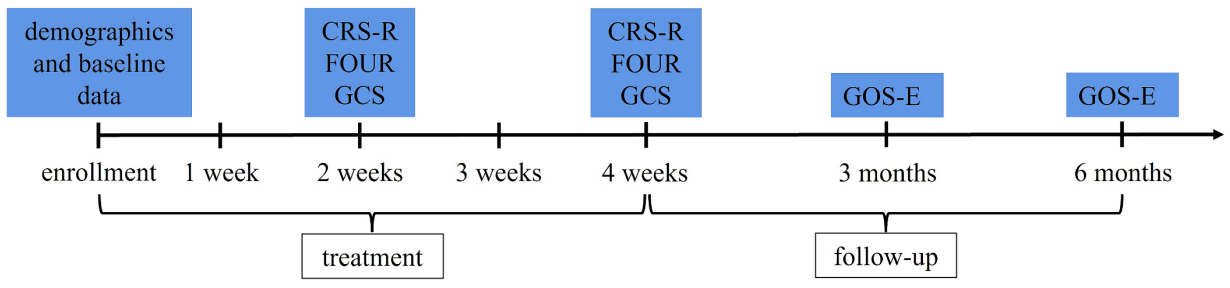

FIGURE 3
Evaluation process. CRS-R, Coma Recovery Scale-Revised; FOUR, Full Outline of Unresponsiveness; GCS, Glasgow Coma Scale; GOS-E, Extended Glasgow Outcome Scale.

Discussion

Despite great efforts in medication therapy, neuromodulation and physical rehabilitation, the successful treatment strategy of DOC remains limited, primarily due to a profound lack of comprehension of the underlying pathophysiology (32). In recent years, there has been a growing interest in VNS as a potential therapeutic approach, encompassing both invasive and non-invasive techniques. The invasive method involves surgically transmitting electrical pulses directly to the exposed cervical vagus nerve. Notably, the vagus nerve asymmetrically innervates the heart, and stimulating the right cervical vagus nerve can result in electrical signals being directly fed into the sinoatrial node, thereby heightening the risk of adverse cardiac events, such as arrhythmia. Conversely, stimulating the left vagus nerve poses a significantly lower risk of such complications. Thus the left vagus nerve is typically the preferred target for invasive method (33). However, this method is expensive and complex to operate. TaVNS, on the other hand, offers an economical, easier to implement and noninvasive alternative. It stimulates the auricular branch of the vagus nerve (ABVN) by targeting the skin of the outer ear, specifically the cymba conchae and cavum conchae (34).

Our previous study demonstrated the efficacy and safety of taVNS through the left ear. It provided the highest level of Class II evidence currently available (24). However, it was a single-center study with a limited sample size. Additionally, as a preliminary study, taVNS was solely administered through the left ear for safety considerations. Nevertheless, some literature indicated that non-invasive stimulation of the ABVN was not associated with adverse cardiac events. This is attributed to its selective stimulation of afferent fibers, which are processed by the brain before reaching the heart, rather than directly activating the heart's pacemaking nodes (35). This effectively mitigates the side effects associated with efferent (visceral) fiber activation. Additionally, several studies have corroborated the security of bilateral taVNS (36, 37). Thereby, our current protocol aims to administer bilateral synchronized taVNS, aiming to boost treatment effectiveness, taking into account that brain damage can occur on the left, right, or both sides in DOC patients.

The ABVN is the only branch of the vagus nerve on the surface of the body, which mainly distributed in the external auditory meatus and concha (cymba conchae and cavum conchae, the cymba conchae is innervated exclusively by the ABVN) (38). The latter is usually considered as the ideal target area for taVNS. The ABVN transmits stimuli from the concha to the spinal trigeminal nucleus and the solitary tract nucleus (39), which is then projected and extended to the cerebral cortex and subcortical regions related to consciousness control (34). Neuroelectrophysiology and neuroimaging play pivotal roles in elucidating the mechanisms by which taVNS affects brain function in patients with DOC. The combination study of taVNS and electroencephalogram (EEG) found that taVNS improved the consciousness level of patients with MCS by enhancing the high-frequency relative power spectrum energy and functional connectivity (FC) of the frontal and parietal lobes (40). In a longitudinal case study (41), the EEG power in the alpha band gradually increased, potentially indicating neural network integration and cortical activity enhancement. Furthermore, a study combining arterial spin labeling-functional magnetic resonance imaging (ASL-fMRI) discovered that preserved auditory function may serve as a prerequisite for taVNS responders among patients with DOC. Additionally, taVNS may activate the salient network, limbic system, and interoceptive system to improve the condition of these patients (42). Yu et al. (19) indicated that TaVNS increased the FC between posterior cingulate/precuneus and hypothalamus, thalamus, ventral medial prefrontal cortex, superior temporal gyrus. Drawing from numerous research findings, Briand et al. (39) proposed a vagal cortical pathways model. They further outlined six possible mechanisms by which taVNS promotes consciousness recovery. In addition, in molecular mechanism research, VNS showed potential for DOC by reducing cell apoptosis, regulating neurotransmitters, decreasing inflammatory responses, and lowering blood–brain barrier permeability (34). However, the exact mechanism is still not fully understood. Further validation research is necessary, as the exact mechanism can provide information for developing more targeted and effective treatment strategies.

In taVNS studies for other diseases, the current intensity was typically determined based on the patient's perceptual threshold [e.g., 200% of the perceptual threshold (43)] or pain threshold [strongest painless stimulus (44)]. However, these methods are not applicable for patients with DOC due to their perception and communication deficits. NCS-R is a validated and highly sensitive tool for assessing the nociceptive pain responses of patients with DOC through motor, verbal and facial aspects (26). In this protocol, we use NCS-R to assess the tolerance of patients to taVNS. Specifically, the current intensity is gradually reduced in steps of 0.5 until the patients exhibit no pain response (NCS-R score < 4).

Although reports indicating that bilateral taVNS has little impact on parasympathetic nerves and is considered safe (36, 37), we will still evaluate its effects on heart rate and blood pressure. HRV serves as a crucial metric for assessing cardiac autonomic regulation by quantifying variations in sinus rhythm (28). Therefore, we will use HRV to measure the impact of taVNS on the sympathetic/parasympathetic balance. Typically, HRV is calculated using a Holter ECG, a process that can be quite intricate. Given that this is a multicenter study, the tools and methods for collecting and analyzing Holter ECG data vary significantly across sub-centers. Additionally, large-sample multicenter trials require procedures that are straightforward and easily executable. Hence, we opt for a solution involving a chest strap coupled with the EliteHRV software. This solution provides acceptable agreement compared to ECG (30, 31). In our protocol, this alternative ensures consistency, simplicity, and operability of multi-center trials.

This protocol still exists some limitations. Firstly, given the complexities of neuroimaging and electrophysiology in multicenter trials, our focus will primarily be on patients' behavioral outcomes, while neglecting neuroimaging or electrophysiology programs. Secondly, due to the difficulties associated with continuously collecting blood pressure data, we will limit our collection to a single measurement before and during taVNS. This approach may somewhat diminish the statistical power compared to continuous blood pressure monitoring. Thirdly, the parameters utilized in this protocol are based on our previous single-center RCT and other relevant studies. There is currently no consensus on the optimal parameters for taVNS. Future studies should focus on determining the optimal parameters for specific patient populations, as well as investigating potential

dose–response relationships and individual factors that may affect treatment outcomes.

In conclusion, the clinical treatment of DOC is challenging. TaVNS is an economical, non-invasive, promising, bottom-up neuromodulation. This protocol aims to provide multicenter, large-sample, and more effective Class II evidence for the efficacy and safety of taVNS for DOC. It will advance the field of treatment options for patients with DOC.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Affiliated Rehabilitation Hospital of Nanchang University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YW: Conceptualization, Writing – original draft. LY: Resources, Writing – review & editing. WL: Resources, Writing – review & editing. QZ: Investigation, Writing – review & editing. MH: Visualization, Writing – review & editing. LZ: Supervision, Writing – review & editing. ZF: Conceptualization, Methodology, Writing – review & editing. YB: Conceptualization, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Closed-loop transcutaneous auricular vagus nerve stimulation for the improvement of upper extremity motor function in stroke patients: a study protocol

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Background: Transcutaneous auricular vagus nerve stimulation (taVNS) has garnered attention for stroke rehabilitation, with studies demonstrating its benefits when combined with motor rehabilitative training or delivered before motor training. The necessity of concurrently applying taVNS with motor training for post-stroke motor rehabilitation remains unclear. We aimed to investigate the necessity and advantages of applying the taVNS concurrently with motor training by an electromyography (EMG)-triggered closed-loop system for post-stroke rehabilitation.

Methods: We propose a double-blinded, randomized clinical trial involving 150 stroke patients assigned to one of three groups: concurrent taVNS, sequential taVNS, or sham control condition. In the concurrent group, taVNS bursts will synchronize with upper extremity motor movements with EMG-triggered closed-loop system during the rehabilitative training, while in the sequential group, a taVNS session will precede the motor rehabilitative training. TaVNS intensity will be set below the pain threshold for both concurrent and sequential conditions and at zero for the control condition. The primary outcome measure is the Fugl-Meyer Assessment of Upper Extremity (FMA-UE). Secondary measures include standard upper limb function assessments, as well as EMG and electrocardiogram (ECG) features.

Ethics and dissemination: Ethical approval has been granted by the Medical Ethics Committee, affiliated with Zhujiang Hospital of Southern Medical University for Clinical Studies (2023-QX-012-01). This study has been registered on ClinicalTrials (NCT05943431). Signed informed consent will be obtained from all included participants. The findings will be published in peer-reviewed journals and presented at relevant stakeholder conferences and meetings.

Discussion: This study represents a pioneering effort in directly comparing the impact of concurrent taVNS with motor training to that of sequential taVNS with motor training on stroke rehabilitation. Secondly, the incorporation of an EMG-triggered closed-loop taVNS system has enabled the automation and individualization of both taVNS and diverse motor training tasks—a novel approach not explored in previous research. This technological advancement

holds promise for delivering more precise and tailored training interventions for stroke patients. However, it is essential to acknowledge a limitation of this study, as it does not delve into examining the neural mechanisms underlying taVNS in the context of post-stroke rehabilitation.

KEYWORDS

stroke, transcutaneous auricular vagus nerve stimulation, VNS, motor rehabilitation, electromyography, closed-loop, heart rate variance

Introduction

The vagus nerve, also referred to as cranial nerve X, stands as the most extensive cranial nerve within the human body. It plays a pivotal role in regulating a multitude of involuntary bodily functions, encompassing heart rate, respiration, digestion, and overall internal homeostasis, functioning as a crucial component of the parasympathetic nervous system (1, 2). Vagus nerve stimulation (VNS) is a method that involves stimulating the vagus nerve using an implantable device. In this procedure, an electrode will be available to the vagus nerve by some operation, and a small device is implanted in the chest to produce specific stimulation. VNS has gained the Food and Drug Administration (FDA) approval as an effective therapy for epilepsy in 1997, as well as for depression in 2005. The most recent FDA approval for VNS is in the realm of motor rehabilitation of upper extremities following ischemic stroke. In recent years, both invasive and non-invasive VNS have garnered increasing attention in the context of ischemic stroke, emerging as a promising new treatment (3).

Recent studies on rat models of stroke (4–9) and stroke patients (10–12) have demonstrated positive effects of VNS on motor rehabilitation. The study by Dawson et al. (10–12) using a randomized double-blind approach showed that the efficacy of VNS paired with motor training was two to three times than that of sham VNS combined with motor training on the upper extremity rehabilitation in ischemic stroke patients. Several mechanisms have been proposed to elucidate the rehabilitative effects of VNS on stroke. These mechanisms include the reduction of neuronal apoptosis (13), the mitigation of infarct size (14), the regulation of neurotransmitter release (15, 16), the modulation of pathways associated with inflammatory factors (17), the enhancement of neurocircuit plasticity (9), the change in the blood–brain barrier permeability (18), and the effects on the hemodynamics (19). In terms of specific mechanisms underlying movement-paired VNS, particularly within the context of the closed-loop VNS as defined in the current study, previous research has shed light on the enhancement and plasticity mechanisms. Dawson et al. (12) have suggested the augmentation of neurocircuit plasticity through VNS treatment when combined with motor rehabilitation training. In a study involving animal models, Meyers et al. (9) found that VNS coupled with rehabilitative training heightened the plasticity within corticospinal motor networks in rats with ischemic lesions, thereby amplifying synaptic connectivity to the musculature of the rehabilitated forelimb. Furthermore, Bowles et al. (15) demonstrated that the application of VNS immediately after a successful movement enhances motor learning through a cholinergic reinforcement mechanism, leading to the selective modulation of M1 neurons. These findings underscore that the impact and mechanisms of VNS on motor rehabilitation may depend on the strategic combination of targeted events, such as motor movements.

However, it should be noted that this invasive VNS requires expensive surgical procedures and has several contraindications (20). Consequently, researchers and clinicians are exploring a non-invasive VNS as a potential alternative intervention. Recently, the use of transcutaneous auricular vagus nerve stimulation (taVNS) as a non-invasive brain stimulation technique in ischemic stroke has received increasing attention [see the review (21)]. This innovative technique involves non-invasive electrical stimulation of the auricular branch of the vagus nerve (ABVN). It has been revealed that this branch projects upstream of the nucleus of the solitary tract (NTS) by traversing the vagal trunk and passing through the jugular ganglion (20, 21). The NTS projects directly or indirectly to a wide range of nuclei, from lower to higher regions, encompassing the parabrachial nucleus, dorsal raphe nucleus, locus ceruleus, hypothalamus, thalamus, amygdala, and hippocampus (1, 22–24). Subsequently, these projections extend further into the cerebral cortex. Compared to VNS, taVNS offers a low-risk, user-friendly, and economic intervention that eliminates the need for surgery and the associated postoperative complications (25, 26).

A small number of research have provided evidence to support the enhancement of motor rehabilitation in stroke patients after taVNS treatment (27–31). A recent meta-analysis has indicated that the efficacy of taVNS in upper extremity rehabilitation for stroke patients can be comparable to that of VNS (26). However, the number of studies is small, and specific taVNS treatment protocols vary. In the study of Wu et al. (31), stroke patients were randomly assigned to receive either real taVNS or sham taVNS, followed by transitional movement training. The taVNS group showed significant improvement in upper limb function, with a 6.9-point improvement in Fugl-Meyer Assessment of Upper Extremity (FMA-UE) and a 6.5-point improvement in Wolf motor function test (WMFT) after the treatment, compared to the sham taVNS group (3.18 and 2.91 points, respectively). In contrast, in another study by Chang et al. (28), each burst sequence of taVNS was administered concurrently with an upper limb movement by mechanical control, leading to significant improvement in spasticity, but no significant difference in FMA-UE (3.10 vs. 2.86) with sham group. Moreover, in another study by Bradan et al. (27), taVNS was administered concurrently with movement training in two different manners. In the paired condition, each burst sequence of taVNS was synchronized with an upper limb movement using an electromyography (EMG)-triggered taVNS system, i.e., a closed-loop system. In the unpaired condition, a programmed taVNS with chronological stimulation was initiated during the movement

training but was not synchronized with movements. FMA-UE scores improved in both groups (5.00 vs. 3.14), with a slightly larger improvement observed in the paired group. Although no statistically significant differences were found from less than 10 patients in each group, this study highlights the potential of utilizing an EMG-triggered closed-loop taVNS system to achieve precise stimulation paired with each movement training. Although these findings indicate taVNS as a valuable tool for post-stroke rehabilitation of acute [0.5 month after stroke (28, 29)], subacute [3 months after stroke (28, 30)], and recovery [6 months after stroke (27, 29)] phases, it remains unknown whether the concurrent application of taVNS and motor movement training is critical for stroke rehabilitation. A comprehensive and random controlled clinical trial with a sufficient sample size is essential to directly validate the clinical effectiveness of taVNS when administered concurrently with motor movements through EMG-triggered closed-loop system. This could provide scientific and data support for the establishment and application of this novel hardware and software system, i.e., EMG-triggered closed-loop taVNS system, in stroke rehabilitation.

In this study, we propose to directly investigate the necessity of the taVNS applied concurrently with motor training for post-stroke rehabilitation. Additionally, we aim to validate the benefits of employing an EMG-triggered closed-loop system in the administration of taVNS treatment during motor training. To achieve this, we have designed two experimental conditions to investigate whether the efficacy of taVNS concurrently with motor movement, i.e., each taVNS burst sequence triggered by the EMG of each motor movement, is superior to that administered sequentially with motor movement. A sham control group has been incorporated to confirm the effectiveness of taVNS treatment. The significance of rehabilitation efficacy within the concurrent group, especially if it significantly surpasses that observed in the sequential and sham groups, would substantiate the necessity for applying taVNS concurrently with motor training as well as support the advantages of the EMG-triggered closed-loop system.

Methods

Participants

This study presents a protocol for a single-center randomized, double-blind controlled trial. To participate in this study, patients are required to meet following specific criteria: (1) Aging between 18 and 80; (2) Having a confirmed diagnosis of ischemic stroke by a qualified clinician in accordance with the guidelines in the Chinese Stroke Prevention and Control Guideline from 2021; (3) In the acute/recovery phase, defined as occurring 2 weeks after the onset of stroke, exhibiting stable vital signs, and showing no progression of the disease within 48 h during this period; (4) Having unilateral upper limb motor dysfunction, are identified as monoplegia or hemiplegia. The participation in this study should be subject to their voluntary cooperation and signing an informed consent form.

Participants will be excluded if they have impairments of upper limb function other than those caused by stroke (e.g., shoulder-hand syndrome), a documented history of psychiatrist-related diseases, severe impairment of cognitive function, inability to cooperate in the rehabilitation training, receiving other neuromodulation rehabilitation treatments simultaneously, presence of cranial metal implants, skull-based pacemakers, the presence of severe spasticity, other serious injuries to the upper extremities, cardiac arrhythmias or other cardiac abnormalities, a history of respiratory disease or disorder (including pneumonia, dyspnea, and asthma), uncontrolled epilepsy or history of epilepsy, a history of vasovagal syncope, or having other contraindications to taVNS.

This study has obtained approval by the Medical Ethics Committee, affiliated with Zhujiang Hospital of Southern Medical University for Clinical Studies (2023-QX-015) and has been registered on ClinicalTrials (NCT05943431).

Sample size

Sample size was determined using $n = 2^*[(Z_{\alpha/2} + Z_{\beta})\sigma/d]^2$ and statistical power analysis software G*Power 3.1. Referencing the size (effect size, Cohen's $d = 0.632$) and parameters of $\alpha = 0.05$, $\beta = 0.85$ observed in the experiment of Dawson et al. (12), the estimated sample size for each group in this study should be 40. Considering the clinical dropout rate of 20%, the sample size was adjusted to 50 for each group.

Randomization and blinding method

A total of 150 participants will be recruited and randomly assigned to three groups (Group 1, Group 2, or Group 3) in a 1:1:1 ratio. Participants will be instructed to randomly select a sealed envelope which contains a digital number ranging from 1 to 150. Those who draw numbers between 1 and 50 will be assigned to Group 1, 51 and 100 will belong to Group 2, and 101 and 150 will be designated to Group 3. The number in the envelope will only be revealed after the follow-up assessments to ensure the blinding of the allocation. This process will be overseen by a research assistant who will not involve in the intervention or data analysis phases. To ensure double-blinding, we will implement three procedures. Initially, we will utilize the same software across all tests, with the number drawn by the patient corresponding to different software settings. These settings will reflect the three distinct conditions. Further, all patients across the three groups will be outfitted with identical EMG sensors and taVNS stimulators. Lastly, we will guide therapists to activate the taVNS three times via a remote control, prior to each type of motor movement training. Consequently, patients in all three groups, particularly the sham group, will experience the sensation of ear stimulation.

Procedures

Each participant will receive 14 treatment sessions on a daily basis for 14 days. During each session, participants will engage in motor movement tasks based on their occupational training protocol prescribed by their therapist. The motor movement tasks are derived from a comprehensive training pool of Dawson et al.'s experiment (2020, 2021, 2023) and consisted of six types of movement tasks, including grasping training, forearm rotations, gross movement training, fine motor training, feeding training,

pinching and griping training. Within each type, there are two to four sub-items tailored for specific functional training purposes. To facilitate and standardize the movement tasks, appropriate aids were designed, and instructional videos were filmed in which the therapist demonstrated each movement task with her left or right hand at the appropriate speed. The duration of each video is approximately 6–7 s.

In Group 1 (concurrent condition), taVNS will be precisely synchronized with motor movements in an EMG-triggered closed-loop system. In Group 2 (sequential condition), participants will receive a session of taVNS treatment followed by motor movement tasks, and the sham taVNS will be paired with motor movements. Lastly, for participants in Group 3 (control condition), sham taVNS will be synchronized with motor movements.

Prior to each session, the therapist will adjust the motor training tasks and determine the number of repetitions for each movement based on each participant's individual abilities and physical condition. Typically, each session will consist of 3–4 tasks, each task comprising 2–3 sub-items. In total, participants are expected to complete approximately 240–300 movements throughout each session.

The motor movement evaluation and training procedures are consistent across all three groups of patients. The experimenter will oversee the participant's adherence to instructional videos when they replicate the movements using affected limb. Prior to each session, the participant will seat in front of a computer, positioning both upper limbs comfortably on the table. The experimenter will sterilize the cymba concha area of the participant's left ear (as shown in Figure 1A) with an alcohol wipe. Subsequently, the taVNS stimulator will be affixed to the left ear, and the electrodes will be firmly attached on both the cymba concha area and the back of the ear. The cymba concha area is considered to be the primary distribution region of the ABVN (25, 32). The amplitude of the taVNS will be adjusted to remain below the patient's pain threshold.

Subsequently, the experimenter will affix two pairs of wireless EMG electrodes to the extensor carpi radialis and flexor carpi radialis muscles of the affected arm to record surface EMG activity during the motor training sessions (as depicted in Figure 1B). The basic quality of EMG signal will be assessed when participants are at rest, and the signal's fidelity during muscle contraction will be visually examined as participants grasp a ball with force. During rest, the EMG signal should exhibit minimal noise, whereas during muscle contraction, EMG spikes corresponding to muscle activity should be evident. Any deviations from these criteria will prompt adjustments to the position of EMG electrodes. With these preparations verified, the experimenter will commence the session by activating a button to calculate the baseline noise level of the EMG signal. The baseline noise level is derived from a 1.5-s period of EMG signals without any voluntary movement before evaluation. Subsequently, participants will be guided through the evaluation and training of each sub-item of the movement task using instructional videos in the software (as shown in Figure 1C). The evaluation before each movement training is to establish the individualized threshold for the subsequent training. The protocol reported by Badran et al. (27) using the EMG-triggered closed-loop taVNS system did not consider the individual EMG thresholds, whereas they input a constant threshold value for the initiation of taVNS. This could sabotage the efficacy of the taVNS due to the differences of threshold parameter from different participants and different motor movements.

As illustrated in Figure 2A, the therapist will initiate the process by selecting the specific type of movement task, specifying the desired number of training repetitions (typically ranging from 30 to 50 rounds), and choosing a sub-item of the task (Figure 2A). The evaluation process has a predetermined integer number of 5, meaning that the movement will be repeated five times. The software records, displays (as depicted in Figure 2B), processes, and decodes EMG signals for both evaluation and training phases. During the evaluation, participants will replicate the prescribed movement for five rounds, guided by the instructional video. Each round comprises preparation, movement, and a rest period (as depicted in Figure 2C). Upon completion of the evaluation, the software will process the EMG signals from the current movement task and generate an evaluation result (as shown in Figure 2D). Participants then transition to the training stage, where they repeat the same movements for the number of rounds specified earlier, as shown in Figure 2D. As demonstrated in Figures 3, 4C, successful execution of the movement by the

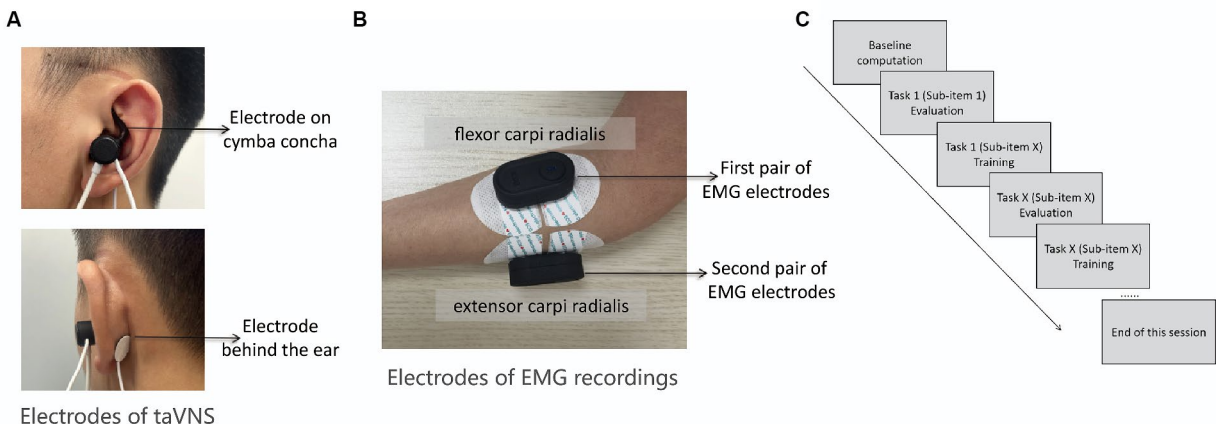

FIGURE 1
(A) The target area of taVNS is ABVN marked by the red ellipse. One of the stimulation electrodes (i.e., the tip of the earplug-shape device) will be fixed on the cymba concha and the other electrode will fixed on the position above the back of earlobe as shown by the arrows above and below; **(B)** Two pairs of wireless EMG electrodes will be attached to the extensor carpi radialis and flexor carpi radialis, respectively; **(C)** Diagram shows the procedures of each session.

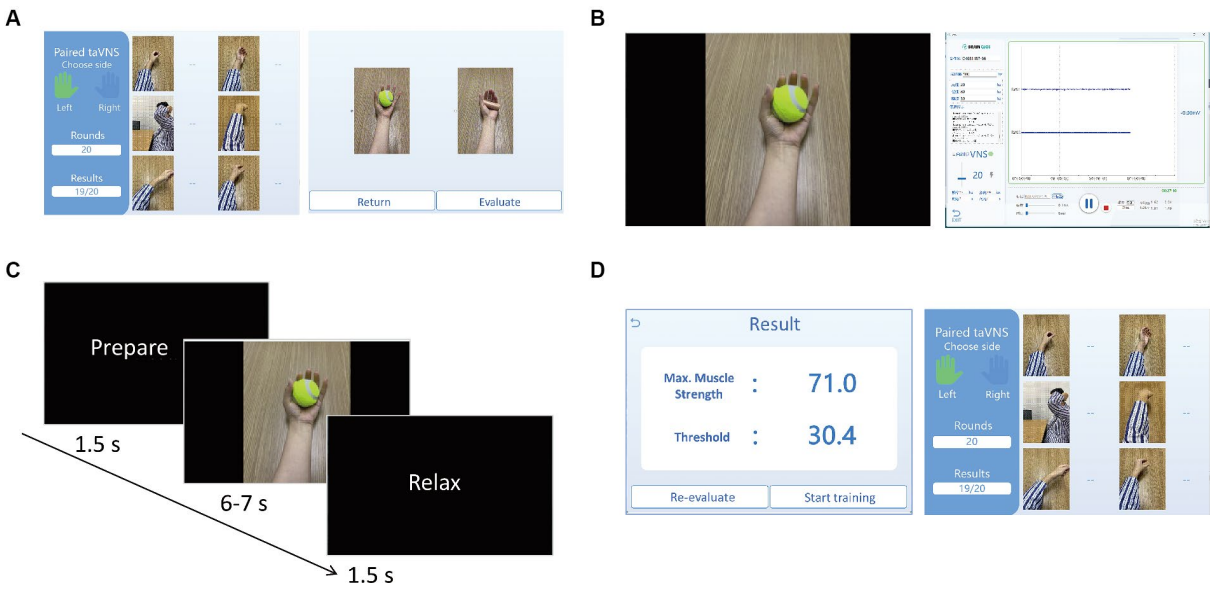

FIGURE 2
(A) The left interface is for selecting affected arm (left or right), the type of motor training task from six GIFs, and the number of the repeated times of the movement (i.e., rounds) by inputting the digital number under Rounds. The right interface is for selecting the sub-item (specific movement) of the motor training task. After selecting the movement and clicking Evaluate, the evaluation process will start to obtain individual threshold value of the movement for triggering taVNS. By clicking Return, it will go back to the left interface; **(B)** The left interface will be presented to the participants for the guidance of the movement training. The right interface will show the EMG waveform. The buttons on the interface can be clicked to calculate the baseline signals, determine the difficulty level, adjust the parameters of taVNS, record and save EMG data; **(C)** The timeline information of the video for guiding the movement training. For each round of the movement, it starts with 1.5 s for preparation, 6–7 s of the motor movement, and 1.5 s of rest; **(D)** After 5 times of the movement evaluation, the EMG algorithm will automatically generate the results of maximum muscle strength and the threshold for the movement training (as shown on the left interface). By clicking the Start training, the training process of the movement will start and the participant will be guided to finish 20 times of the movement according the number of Rounds. After finishing the total rounds, the right interface will show the training results, i.e., the successful rate of the movement triggering taVNS.

participant, as determined by EMG features surpassing the threshold parameter, will trigger a burst sequence of taVNS. Such a round of movement will be classified as a successful one (for detailed analysis, refer to the Data Processing section and Figure 4). The software accumulates the successful movement rounds and displays the total count in the Results section (Figure 2D).

For participants in Group 1, the amplitude level of the taVNS for each burst sequence remains the same as the pre-training setting. Conversely, in Group 2 and Group 3, the amplitude level of taVNS will be set to zero. According to Dawson et al. (12), to maintain the blindness of participants regarding the experiment's objectives, the experimenter will activate the taVNS three times using a remote control prior to each type of motor movement training.

Each session lasts approximately 45 to 60 min and the success rate of movements triggering taVNS should reach 85% or higher. The therapist will closely monitor for compensatory actions during each movement task, and participants will be instructed to rest if fatigue or compensatory actions are observed. Specific training tasks for each session will be adjusted according to the participant's rehabilitation progress.

Outcome measures

The primary outcome measures include assessment of treatment efficacy by evaluating motor functions via FMA-UE. It is a clinical tool to assess motor function and recovery with upper limb impairments resulting from stroke or neurological conditions in individuals. It quantifies motor skills, coordination, and reflexes through a structured examination that encompasses various subscales assessing different aspects of motor function, sensation, and coordination in the upper limbs. Drawing on the study of Dawson et al. (12), we established that a clinically significant response is defined as an upgrade of six points or more in the FMA-UE score. This basis is anchored in earlier research findings that linked an increase of 5.25 points with a substantial improvement, reflecting more than a 50% enhancement in arm functionality.

In addition to the primary outcome, this study will consider several secondary measures, including the WMFT, Brunnstrom recovery stages (BRS), Barthel Index (BI), the Hong Kong version of the Functional Test for the Hemiplegic Upper Extremity (FTHUE-HK), and EMG and electrocardiogram (ECG) features. WMFT and FTHUE-HK are designed to evaluate upper extremity motor function with neurological or musculoskeletal impairments. The BRS is a framework that describes the typical progression of motor recovery in stroke patients. It consists of six stages ranging from flaccidity to near-normal movement patterns. BI is a clinical assessment tool used to measure an individual's ability to independently perform activities of daily living (ADLs). EMG will be recorded automatically by a computer software along with each treatment session, and the ECG features, including heart rate variability (HRV) and heart rate (HR) will be recorded before and after each taVNS treatment session as biomarkers reflecting the activation of vagal tone (33, 34).

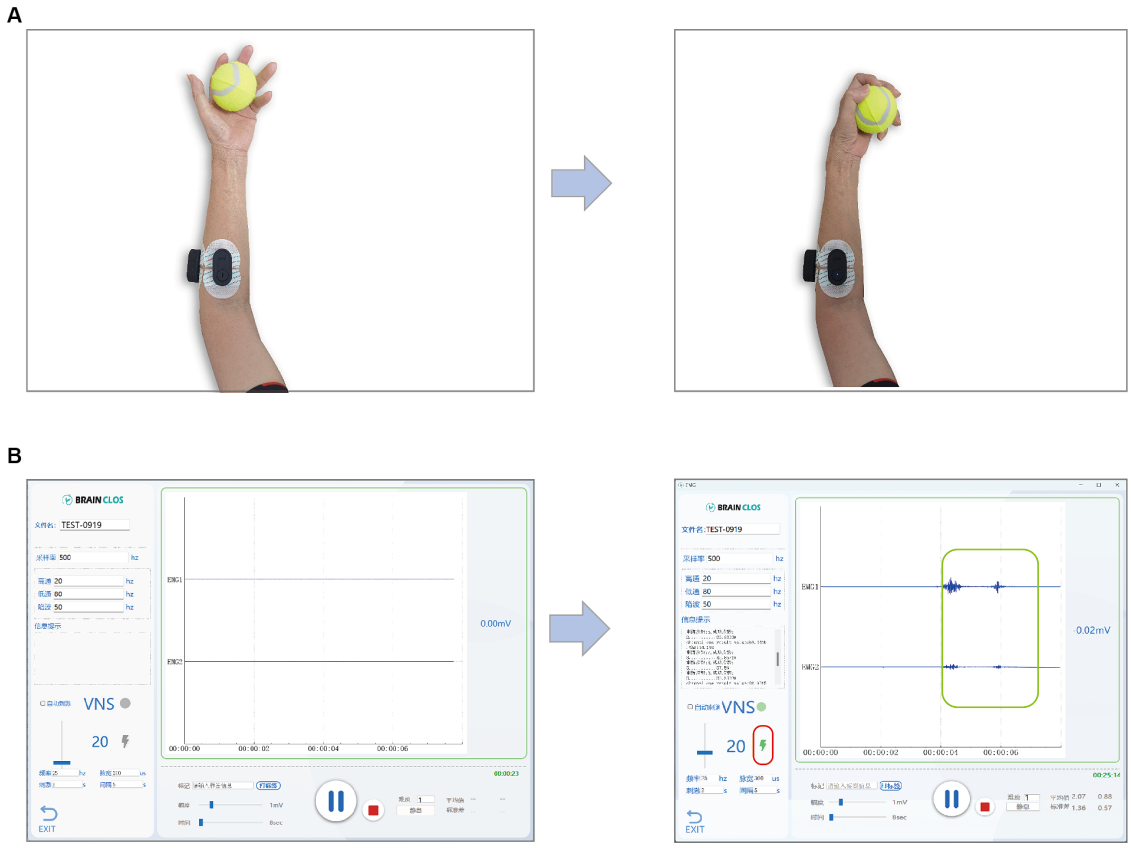

FIGURE 3
(A) A participant is doing motor training while recording the EMG. The left picture shows the preparation of the grip movement or the position after finish once of the movements, and the right picture shows the accomplishment of the movement. **(B)** Software show the EMG and indicate the taVNS triggered by the successful motor movement. The left picture shows the EMG while the participant is on preparation stage or rest stage. The right picture shows the EMG while the participant is doing the movement task. The green rectangle highlights the EMG signals reflecting the muscle contraction during the movement and lightening bolt symbol highlighted by the red rectangle indicates that a taVNS is triggered by the EMG feature as it passes the threshold parameters.

Primary and secondary outcome measures, except for EMG and ECG, will be assessed the day before or at the latest the day after the first session and again after the 14th session. Additionally, two follow-up assessments will be scheduled, one 30 days and another 90 days following the conclusion of the last training session. To ensure consistency and reliability, each participant will be accessed by the same therapist before training, immediately after training, and during scheduled follow-up periods. EMG and ECG signals will be recorded and saved for each session.

Equipment and parameters

The taVNS device (BC102-IV, BrainClos, Shenzhen, China), EMG (BC107, BrainClos, Shenzhen, China) and ECG (BC116, BrainClos, Shenzhen, China) used in this experiment will be provided by Shenzhen BrainClos Technology Co., Ltd. The stimulation parameters of the taVNS are as follows: a frequency of 25 Hz, a pulse width of 300us, and a stimulation intensity ranging from 0 to 6 mA. This intensity can be finely adjusted across 60 levels, with each level representing a 0.1 mA increment. The stimulation intensity will be customized based on the participant's tolerance and comfort level. In Group 1, each EMG-triggered taVNS burst lasts for 3 s. The total pulses will depend on the number of successful movements. In Group 2, each taVNS session lasts 31.25 min, cycling through 3 s of stimulation followed by 4.5 s rest. The total number of pulses will be 18,750.

Both EMG and ECG have a sampling rate of 500 Hz, and high precision signals are obtained through a 24-bit AD converter. The two devices are designed to use Bluetooth communication with very low noise to acquire uV-level electrophysiological signals. Bluetooth minimizes signal artifacts from patient movements and avoids industrial frequency interference at 50 Hz. EMG and ECG will be preprocessed and calculated for triggering taVNS or evaluating biomarker purposes, respectively.

EMG and ECG data processing

The EMG data will be processed in real time during the evaluation and training phases. The prepossessing steps include filtering, rectification, and integration. First, EMG data will be filtered online within the bandpass range of 20-80 Hz, along with a notch filter at 50 Hz (illustrated in the left panel of Figure 4A). Subsequently, the filtered data will be rectified (as depicted in the middle panel of Figure 4A) and integrated (as shown in the right panel of Figure 4A).

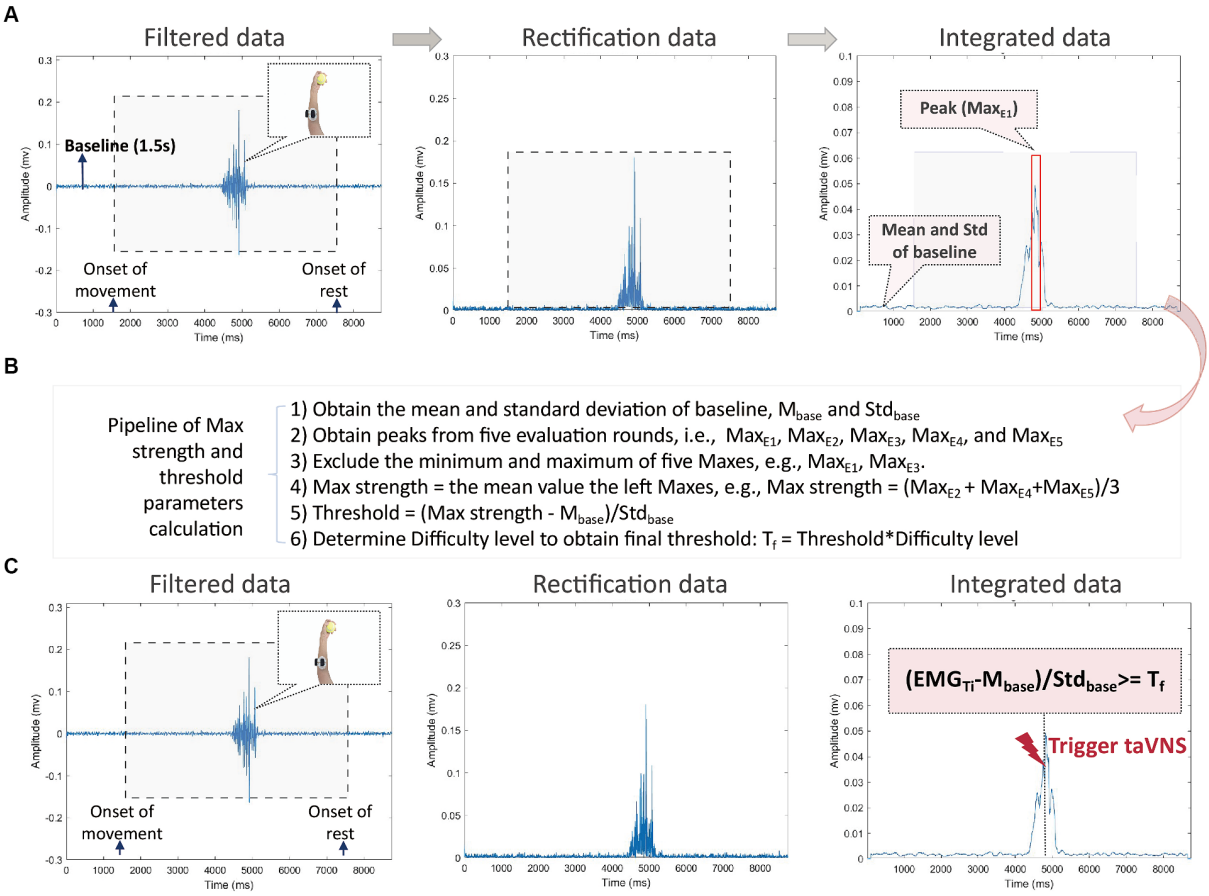

FIGURE 4
(A) The pipeline of data analysis during movement evaluation stage. The data of each round are marked for the onset of movement (i.e., the start of the video) and the onset of the rest (i.e., the end of the video). The baseline is defined as a 1.5-s period without any movement before the first round, such as the Baseline highlighted on the left picture. The gray rectangle marks for the period of movement (i.e., video time). Raw data are filtered (left picture), rectified (middle picture), and integrated (right picture). From the integrated data, the mean and standard deviation values are calculated from the 1.5 s of the baseline. The red rectangle highlights the peak EMG (noted as Max_E), i.e., the maximum mean EMG value during movement; **(B)** The pipeline of maximum strength and threshold parameters calculation from evaluation data. Six steps are listed; **(C)** The pipeline of data analysis during movement training stage. The EMG (noted as EMG_{Ti}) is checked online to trigger taVNS. If (Max_{Ti} – M_{base}/Std_{base} ≥ T_f, taVNS) (real or sham) will be triggered, otherwise no taVNS (real or sham) will be triggered.

During integration process, we will use a moving time window of 50 ms to calculate the mean values of the EMG signal over a 100 ms interval.

ECG realtime processing will be employed to denoise the data, identify the R-R interval, and calculate HR and HRV. HRV will be represented in both the time domain and frequency domain. The chosen index of HRV in time domain is the root mean square of successive R-R interval differences (RMSSD), which reflects the beat-to-beat variance of HR and serves as a primary measure for estimating vagally mediated changes in HRV (35). The ratio of low-frequency (LF) power to high-frequency (HF) power will be used as a HRV index in the frequency domain. This ratio may provide an estimate of the balance between sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) activity.

Threshold parameters to trigger taVNS

As shown in Figure 4B, we will promptly compute the threshold parameters based on the integrated evaluation data after the evaluation phase. The data processing involves the following specific steps:

1. Initially, we calculate the mean (M_{base}) and standard deviation (Std_{base}) of the integrated data collected during a 1.5-s baseline period.
2. We identify and extract the peaks from five evaluation rounds, denoted as Max_{E1}, Max_{E2}, Max_{E3}, Max_{E4}, and Max_{E5}.
3. To ensure robustness, we discard both the minimum and maximum peaks among the five, for instance, eliminating Max_{E1} and Max_{E3}, which correspond to the minimum and maximum peaks.
4. Subsequently, we determine the maximum strength, denoted as Max strength, by calculating the mean value of the remaining three peak values, such as Max strength = (Max_{E2} + Max_{E4} + Max_{E5})/3.
5. The original threshold is then computed using the formula Threshold = (Max strength − M_{base})/Std_{base}.
6. Considering factors like performance decay and muscle fatigue during training, we derive the final threshold parameter (T_f) as

a relative threshold by adjusting the threshold with a difficulty level.

Triggering taVNS from integrated training data

For each training movement, the EMG data will undergo the same prepossessing steps as the evaluation data. Each integrated data point (EMG_{Ti}) will be processed using $(EMG_{Ti} - M_{base})/Std_{base}$ to derive a parameter for initiating taVNS. If this parameter exceeds T_f, taVNS will be activated.

To ensure the accuracy and reliability of the synchronization of taVNS and the motor movements (decoded as the EMG parameters), we conducted a comprehensive examination. This involved assessing the time precision of the software governing taVNS and EMG, the processing time for EMG data, the duration for triggering taVNS from the software, and the time delay of EMG signals from wireless electrodes. Importantly, none of these factors are expected to impact the synchronization of stimulation and motor movements in the current EMG-triggered closed-loop taVNS system.

Statistical analyses

The critical level of significance for all statistical analyses will be set to $p < 0.05$. The analyses will be carried out by the Matlab and R statistical software packages.

Analysis of main endpoint indicators

Main indicators will be examined using analysis of variance (ANOVA), paired samples t-test, and independent samples t-test. Prior to conducting inferential statistics, Kolmogorov–Smirnov (K-S) tests will be employed to assess the normality of the measurement data. In cases where the data deviate from a normal distribution, transformation methods will be applied. Specifically, logarithmic transformation may be employed for data exhibiting extreme skewness, while the square root transformation can be adopted for data displaying moderate or small skewness. To evaluate the primary efficacy (i.e., the change in FMA-UE scores), a paired samples t-test will be performed within each group before and after the treatment sessions. This analysis will help determine if there is a significant improvement in upper limb function after taVNS treatment. The FMA-UE scores before and after the treatment sessions will be subtracted to calculate the FMA-UE improvement scores, representing the primary treatment effect. A one-way three-level ANOVA will be employed to examine the differences in the primary treatment effect among the three groups: concurrent, sequential, and control. Independent samples t-tests will be conducted to compare the primary treatment effects of the concurrent condition with the control condition and the sequential condition with the control group, thereby determining the treatment effects of the two experimental groups. Additional independent samples t-tests will be performed on the primary treatment effects of the concurrent and sequential conditions to assess the potential benefits of concurrent taVNS and movements. Wilcoxon signed-rank test and the Friedman test will be performed for the ordinal outcome measures. The effect sizes of the treatment effects in each group (Cohend' s d) and those of the differences in treatment effects among three groups (Eta-squared, η^2) will be documented.

Analysis of secondary endpoint indicators

Secondary endpoint indicators will be statistically examined by ANOVA, concurrent samples t-test, and independent samples t-test. The statistical results will be corrected based on Bonferroni's principle as this statistical operation requires multiple comparisons, and there will be a bias of Alpha inflation. The scores for WMFT, BRS, BI, and FTHUE-HK before and after treatment sessions will be analyzed using the same approach as for the primary endpoint indicators. The muscle strength and threshold values calculated from EMG signals during the first and last sessions from the same motor movements will be subtracted and averaged for each participant. In cases where no identical motor movement between the first and last sessions, additional motor movements identical to the first session will be evaluated in the last session. ANOVA will be utilized to analyze the changes in strength and thresholds across the three groups, exploring the effects of taVNS on EMG features of motor movements. The HRV values before each session will be subtracted from those after each session and averaged for each participant. ANOVA will be employed to analyze the HRV changes across the three groups to examine the effects of taVNS on HRV. The corresponding effect sizes of secondary indicators will also be analyzed.

Analysis of data from follow-up evaluations

Data collected during follow-up evaluations will exclusively consist of questionnaires, with no inclusion EMG and ECG data. The evaluation of primary and secondary endpoint indicators will follow the same procedures outlined earlier during the follow-up assessments.

Expected results and discussion

Currently, no studies have systematically examined the necessity of taVNS applied concurrently with motor training for stroke rehabilitation. Nor have studies provided direct clinical evidence for the benefits of pairing taVNS with movement by decoding EMG signals during motor training. Previous studies have indicated that pairing VNS (10–12) or taVNS (27, 28, 30) with rehabilitative training can enhance motor function recovery. Whereas a study by Wu et al. (31) demonstrated that taVNS treatment prior to regular motor training could improve motor functions. Recent research by Badran et al. (27) highlighted the benefits of movement-synchronized taVNS by decoding EMG signals compared to simple combination of taVNS and movements. However, their study was not designed with a sham control group and the number of subjects per group was limited to less than 10. In comparison, our study can validate the experimental results in a larger sample size with a sham control group. On the other hand, the results will highlight the value of the EMG-triggered closed-loop system for VNS and taVNS treatment for motor rehabilitation, which could be labor-saving compared to the original protocol by Dawson et al. (12) where a therapist constantly monitors each motor movement and trigger the taVNS manually. This study represents a pioneering effort in directly comparing the impact of concurrent taVNS with motor training to that of sequential taVNS alongside motor training.

We anticipate that upper limb motor function could be significantly enhanced in concurrent group compared to the other two groups, as indicated by the FMA-UE scores. Furthermore, we expect that the results of secondary outcome measurements will be consistent with those of FMA-UE scores. These findings are expected to provide direct evidence to support the advantages of applying taVNS concurrently with motor movement training, instead of employing them separately. On the other hand, we expect the result pattern of EMG features to be consistent with the changes in the questionnaire scores of primary and secondary measurements. After the treatment sessions, the muscle strength and the threshold of the motor movements will be increased. These results will provide physiological evidence for the rehabilitation of motor function, which will be in line with the findings from Chang et al. (28).

Regarding the features derived from ECG data before and after taVNS treatment sessions, a noteworthy reduction in HR is expected, as well as in LF/HF power ratio, and an increase in the RMSSD in the sequential group. For the concurrent group, the interleaved motor movement training may stimulate the sympathetic system, therefore we do not expect significant changes in HR, LF/HF power ratio, and RMSSD after treatment with taVNS. In the sham control group, no substantial changes are expected in ECG features. These findings, particularly in the sequential group, will validate the modulation effect of parasympathetic activity within the vagus nerve system through the transcutaneous stimulation of ABVN.

Although the ECG features can be utilized to assess vagal tone activation and the EMG features may reflect motor function progress and the sympathetic tone to some extent, these results may not sufficiently unveil the neural mechanisms underlying the rehabilitative effects of EMG triggered closed-loop taVNS on motor deficits. Therefore, additional electrophysiological assessments such as sympathetic skin responses, motor evoked potentials via transcranial magnetic stimulation (TMS), vagus somatosensory evoked potentials (VSEP) using electroencephalography (EEG) recordings (36, 37), or TMS-evoked potentials (TEP) should be considered. Designing studies to explore modifications in spinal ascending and descending tracts and circuits would provide valuable insights into the modulation of motor control and corticospinal motor networks following taVNS. Functional magnetic resonance imaging (fMRI) assessing changes in brain activity and the default mode network before and after treatment sessions or during taVNS intervention is equally crucial (38, 39). Collectively, insights gathered from these multidimensional perspectives would offer a comprehensive understanding of the mechanisms underlying closed-loop taVNS for stroke rehabilitation.

TaVNS, especially in the context of closed-loop taVNS, has the potential to integrate a broader spectrum of rehabilitation strategies beyond traditional motor physical therapy, including the application of Brain-Computer Interface (BCI) technology. Within the domain of stroke rehabilitation, BCI technology has employed motor imagery (MI) training with surface EEG recordings, incorporating visual or electrical feedback (e.g., functional electrical stimulation, FES) (40, 41). The real-time nature of the feedback makes BCI a valuable tool for promoting motor recovery. The rehabilitative benefits of BCI protocol are linked to active rehabilitation and brain neural plasticity, aligning with prior findings on the reinforcement mechanisms underlying taVNS for motor rehabilitation (9, 12, 15). Integrating taVNS as additional feedback, either alongside or following visual feedback or FES during MI and BCI training, could offer a novel intervention to enhance the overall effectiveness of stroke rehabilitation. This approach would be particularly valuable for stroke patients lacking adequate muscle strength to participate in the current study, thereby expanding the inclusivity and effectiveness of stroke rehabilitation interventions.

Conclusion

This study will provide direct evidence for the necessity and advantages of the concurrent application of taVNS and motor movement training in the rehabilitation of upper extremity motor function after stroke. The incorporation of an EMG-triggered closed-loop taVNS system has enabled the automation and individualization of both taVNS and diverse motor training tasks—a novel approach not explored in previous research. This technological advancement holds promise for delivering more precise and tailored training interventions for patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Medical Ethics Committee, affiliated with Zhujiang Hospital of Southern Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

X-ZX: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. RL: Supervision, Project administration, Methodology, Conceptualization, Writing – review & editing, Writing – original draft, Investigation. CX: Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. SL: Writing – review & editing, Supervision, Methodology, Investigation, Data curation. MY: Writing – review & editing, Software, Methodology, Investigation. HZ: Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. XH: Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. JM: Writing – review & editing, Supervision, Software, Methodology, Investigation. QX: Writing – review & editing,

Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

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Conflict of interest

X-ZX is the co-founder of BrainClos company. SL is the RA of BrainClos company.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Dominance of attentional focus: a comparative study on its impact on standing postural control in healthy younger and older adults

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Introduction: Attentional focus is a phenomenon in which shifting the focus of attention alters performance of standing postural control. It can be categorized as internal focus (IF), which directs attention to the body parts, or external focus (EF), which directs attention to the external environment. Although attentional focus that improves standing postural control in younger people exhibits individual dominance, the dominance of attentional focus in standing postural control in older adults remains ambiguous. Therefore, this study aimed to compare the dominance of attentional focus in standing postural control between healthy younger and older adults, a crucial step for understanding the aging process.

Methods: The participants performed a standing postural control task under the IF and EF conditions. Based on the condition during which they exhibited superior performance, the participants were divided into two groups: IF-dominant and EF-dominant. The standing postural control performance in each group under the IF and EF conditions was subsequently compared.

Results: The results showed that the participants, encompassing both younger and older adults, were divided into the IF-dominant and EF-dominant groups, confirming the dominance of attentional focus. The performance under the EF condition in older adults was also influenced by the dominance of attentional focus.

Conclusion: These results highlight the potential importance of intervention methods based on the dominance of attentional focus, providing valuable insights into future research and clinical practice.

KEYWORDS

attentional focus, dominance, older adults, standing postural control, attentional function

1 Introduction

Falls among older adults, hindering their health and increasing the economic burden on society, pose a significant public health problem (World Health Organization, 2021). In recent years, particularly with the global aging of the population, the number of older adults who experience falls has been increasing, necessitating proactive preventive interventions (Pinheiro et al., 2022; Salari et al., 2022). Impaired standing balance is a major risk factor for falls. Therefore, the effectiveness of exercise interventions in improving balance disorders has been extensively investigated (Granacher et al., 2011; Lesinski et al., 2015; Loureiro et al., 2021). Perturbation-based balance training that induces reactive

balance control has recently been reported to improve standing postural control ability (Gerards et al., 2017). Furthermore, advancements in science and technology have led to the development of new intervention methods, such as virtual reality (Chen et al., 2021) and vision-related trainings (Mak et al., 2021), aimed at improving the effectiveness of exercise interventions. Consequently, there is ongoing development and refinement of new fall prevention strategies for older adults. Continuing to explore additional methods to mitigate the risk of falls in this demographic is imperative.

A decline in attentional function has been observed to have a negative influence on standing balance (Woollacott and Shumway-Cook, 2002). Compared with younger adults, older adults' standing postural control performance is reduced by attentional cost demands, such as dual tasks (Maylor and Wing, 1996; Boisgontier et al., 2013). This suggests that standing postural control in older adults requires more attentional resources and reduced attentional function increases postural sway.

Performance varies depending on the focus of attention during movement. This phenomenon, referred to as attentional focus, comprises two types of attention: internal focus (IF) and external focus (EF) (Wulf et al., 2010; Sawai et al., 2022a). IF refers to attention focused on a body part, such as the hand or foot, whereas EF refers to attention directed toward the external environment, such as a pointing cursor or an item. Many previous studies have reported that EF enhances performance compared with IF when the same postural control task is performed under both IF and EF conditions (Park et al., 2015). The effectiveness of the EF in healthy younger adults has been confirmed in a postural holding task on an unstable board (Chiviacowsky et al., 2010) and using a dynamic postural control task (Wulf et al., 2004). The effectiveness of EF in postural control in older and younger adults has also been reported (Chen et al., 2023). Although several studies have demonstrated the effectiveness of EF in postural control, we found individual dominance of performance-enhancing attentional focus in standing postural control in healthy younger adults (Sawai et al., 2022b, 2023). This suggests that there is an IF-dominant group with high IF performance and an EF-dominant group with high EF performance. Nevertheless, the dominance of attentional focus in standing postural control in older adults, whose cognitive and attentional functions are reduced compared to younger adults (Lacour et al., 2008), has not been clarified. Elucidating this, standing postural control training that takes into account the dominance of attentional focus could be devised to prevent falls in older adults.

Therefore, this study had the following objectives: To assess (i) the dominance of attentional focus in standing postural control in healthy younger and older adults and (ii) the relationship between attentional function and standing postural control performance under IF and EF conditions. In this study, we hypothesized that the dominance of attentional focus in standing postural control would be confirmed in older adults as well as in younger adults. In addition, since attentional function declines with age (Lacour et al., 2008), we expected that standing postural control performance under attentional focus conditions, particularly in older individuals, would be affected.

2 Materials and methods

2.1 Participants

Thirty-one healthy younger adults under 26 years of age (age: 21.71 ± 0.46 years, height: 164.48 ± 8.42 cm, body weight: 56.44 ± 12.56 kg) and 31 healthy older adults over 65 years of age (age: 73.52 ± 4.41 years, height: 156.87 ± 7.21 cm, body weight: 48.99 ± 15.32 kg) were recruited in this study. The healthy younger participants group included 11 men and 20 women, while the healthy older participants group comprised five men and 26 women. The inclusion criteria were: Healthy participants (i) with normal or corrected-to-normal vision; (ii) without fractures, injuries, lacerations, or motor paralysis limiting limb mobility; and (iii) with the ability to stand and walk without assistance. The Japanese version of the Rapid Dementia Screening Test (Adachi et al., 2021) was administered to older adults; participants with a score of < 8 points were excluded on suspicion of cognitive impairment (Kalbe et al., 2003). The sample size was determined using WebPower and R (Zhang and Yuan, 2018). With an effect size of 0.30, Numerator degree of freedom = 1.00, $\alpha = 0.05$, and power $(1 - \beta) = 0.80$ at a confidence level of 95%, the determined sample size for both the two-factor analysis of variance (ANOVA) and the three-factor ANOVA was 45. All participants provided informed consent, and the study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Ethics Committee of Kyoto Tachibana University (approval no. 23-59).

2.2 Study protocol

This study employed a randomized crossover design (Figure 1). Initially, the participants were evaluated using the Trail Making Test Part A (TMT-A). Next, the participants were instructed to perform a standing postural control task under the control condition, followed by tasks under the IF and EF conditions, in a randomized sequence. To ensure that the preceding condition did not influence the subsequent one, a washout condition similar to the control condition was established between the tasks under the IF and EF conditions.

2.3 Measures

The attentional function was evaluated using the TMT-A (Spreen and Strauss, 1998; Tombaugh, 2004). Using the TMT-A, the participants were required to connect numbers 1–25 that were randomly placed on paper in an ascending order as quickly as possible. The time taken to complete the task was measured in seconds, with shorter times indicating superior attentional function.

The index of postural stability (IPS) (Suzuki et al., 2018; Sawai et al., 2022b, 2023) was used to assess standing postural control ability. For this purpose, the participants were asked to stand barefoot on a stabilometer (T.K.K. 5810; Takei Kiki Kogyo Co., Ltd., Niigata, Japan) with their arms crossed in front of their chests. The

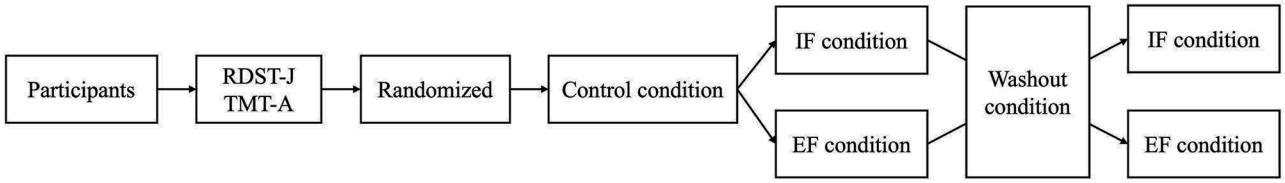

FIGURE 1
Study protocol. This study employed a randomized crossover design. The participants were asked to perform the TMT-A, followed by a standing postural control task. The standing postural control task was performed in a randomized sequence under the IF and EF conditions after the control condition. A washout condition was set between the IF and EF conditions. TMT-A, trail-making test part A; IF, internal focus; EF, external focus.

stabilometer measured the sway of the center of gravity within an area of 360 mm × 360 mm. The sampling rate was set to 100 Hz. Monitors were placed at 1.5 m in front of the participant, such that their centers were at the eye level of the participants. The center-of-gravity cursor, as measured by the stabilometer, was projected in real-time (Figure 2). Regarding the IPS measurements, the sway of the center of gravity was first measured for 10 s in the center position. Then, the center of gravity was held in a posture with maximum movement to the front, back, left, and right, and the sway of the center of gravity was measured for 10 s in each direction. The areas of postural sway and stability limit were calculated from the measured center-of-gravity sway data in five directions (Figure 3). IPS was calculated using the following equation:

$$IPS = \log \frac{Area\ of\ stability\ limit + Area\ of\ postural\ sway}{Area\ of\ postural\ sway}$$

Here, the "area of postural sway" was defined as the average of the rectangular area of the center-of-gravity sway in each direction, serving as an indicator of the ability to hold the center-of-gravity in a fixed position. The "area of stability limit" was calculated using the formula "distance between front and rear center-of-gravity movement of anterior and posterior positions × distance between right and left center-of-gravity movement of right and left positions." The area of the stability limit reflected the ability to move the center of gravity within the base of the support. A high IPS value also implied a high-standing postural control performance.

In this study, the target of attention was manipulated by the verbal instructions for each condition. Under the control and washout conditions, the verbal instruction was "lean front (back, right, left) and try not to move as much as possible," without reference to the object of attention. Under the IF condition, attention was focused on the foot with the instruction, "Pay attention to the weight on the foot; put your weight on the front (back, right, left) of the foot and try not to move it as much as possible." In contrast, under the EF condition, the participant's attention was focused on the center-of-gravity cursor on the monitor with the instruction, "Pay attention to the center-of-gravity cursor projected on the monitor, move the point up (down, right, left) and try not to move it as much as possible" (Sawai et al., 2022b, 2023). Immediately after the IF and EF conditions, the participants self-evaluated their ability to focus their attention as per the verbal instruction on a numerical rating scale (0–100). The participants who scored <60 were considered not to have focused their attention as per the verbal instruction and were consequently excluded from the analysis (Richer et al., 2017; Sawai et al., 2022b, 2023).

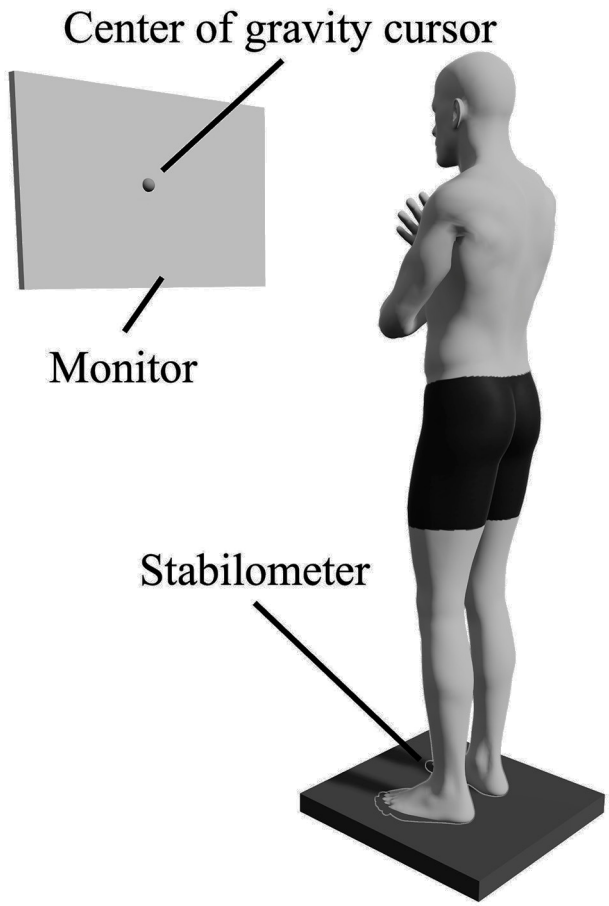

FIGURE 2
Experimental setup. The participants were instructed to stand barefoot with their arms crossed over their chests on the stabilometer. A monitor was placed in front of the participant at eye level, and it displayed the center of gravity cursor in real time.

Based on the IPS results, the participants who achieved a higher IPS under the IF condition than under the EF condition were defined as the IF-dominant group. Conversely, the participants who achieved a higher IPS under the EF condition than under the IF condition were defined as the EF-dominant group (Sakurada et al., 2019b; Sawai et al., 2022b, 2023).

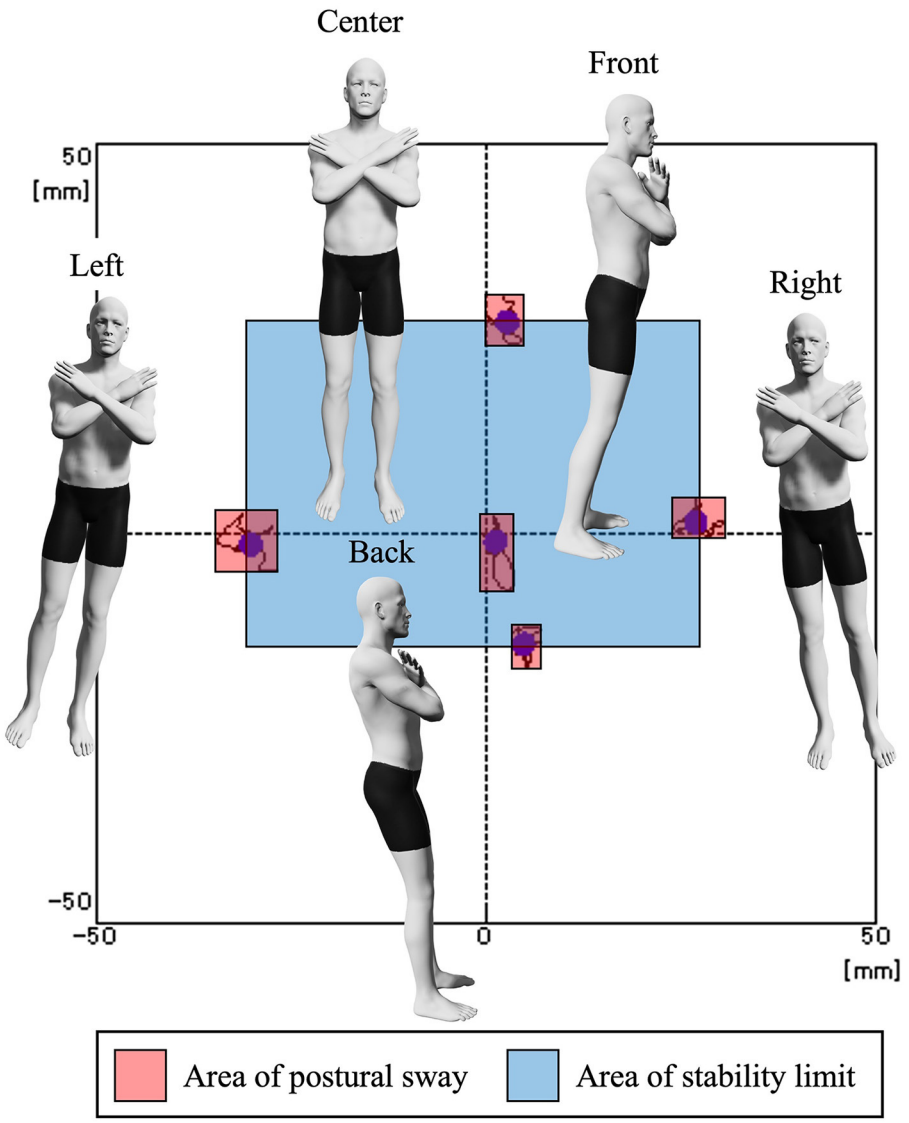

FIGURE 3
Index of postural stability. The participants were first examined for the sway of the center of gravity at the center position. Next, the participants had to hold a posture in which the center of gravity was shifted maximally to the front, back, right, and left. The area of postural sway and the area of stability limit were calculated from the center of gravity sway data in five directions, and the IPS was calculated.

2.4 Statistical analyses

First, a chi-square test was used to compare the sex ratio between younger and older adults. After that, the normality of all data was confirmed using the Shapiro–Wilk test. The IPS was then compared using a mixed-design 2-way analysis of variance (ANOVA) using two factors: age (younger adults, older adults) and condition (IF condition, EF condition). In addition to this, the IPS for each condition was compared using a mixed-design 3-way ANOVA using three factors: attentional focus dominance (IF-dominant group, EF-dominant group), age (younger adults, older adults), and condition (IF condition, EF condition). We conducted a chi-square test to compare the distribution of participants based on the order of conditions performed (IF condition first, EF condition first) and the dominance of attentional focus (IF-dominant group, EF-dominant group). Furthermore, the TMT-A times of participants were compared using a 2-way ANOVA with two factors: dominance of attentional focus (IF-dominant group, EF-dominant group) and age (younger adults, older adults). Bonferroni *post-hoc* tests were used for multiple comparisons of all ANOVAs. The relationship between the IPS and TMT-A times for each condition was examined using Pearson's correlation analysis separately for the younger IF-dominant group, the younger EF-dominant group, the older IF-dominant group, and the older EF-dominant group. SPSS version 29.0 was used for statistical analysis. The statistical significance level was set at 5%.

3 Results

The chi-square test found no significant differences in the number of male and female participants

between younger and older adults ($\chi^2 = 3.03$, $p = 0.08$).

The Shapiro–Wilk test showed that all data were normally distributed ($p > 0.05$). Comparing the IPS under the IF and EF conditions between younger and older adults, there was no significant interaction between the two factors of age and condition ($F = 1.52$, partial $\eta^2 = 0.03$, $p = 0.22$). There was a significant main effect of age ($F = 42.64$, partial $\eta^2 = 0.42$, $p < 0.01$). The *post-hoc* test results showed that the IPS under both the IF and EF conditions was significantly higher among younger adults than among older adults ($p < 0.01$). However, there was no significant main effect of the condition ($F = 2.45$, partial $\eta^2 = 0.04$, $p = 0.12$) (Table 1).

The IPS under the IF and EF conditions was compared and grouped into IF-dominant and EF-dominant groups. Among the younger adults, 16 belonged to the IF-dominant group and 15 to the EF-dominant group. In comparison, among the older adults, 19 belonged to the IF-dominant group and 12 to the EF-dominant group (Figure 4). A comparison of the IPS with a 3-way ANOVA revealed no significant interaction between the three factors of age, dominance of attentional focus, and condition ($F = 3.07$, partial $\eta^2 = 0.05$, $p = 0.09$). Similarly, there were no significant interactions between age and dominance of attentional focus ($F = 0.65$, partial $\eta^2 = 0.01$, $p = 0.42$) or between age and condition ($F = 0.59$, partial $\eta^2 = 0.01$, $p = 0.45$). However, a significant interaction was observed between the dominance of attentional focus and condition ($F = 77.58$, partial $\eta^2 = 0.57$, $p < 0.01$). *Post hoc* tests showed that the IF-dominant group had a significantly higher IPS under the IF condition than that under the EF condition; the EF-dominant group had a significantly higher IPS under the EF condition than that under the IF condition for both younger and older adults ($p < 0.01$). In addition, the IPS under the EF condition was significantly higher in the EF-dominant group than in the IF-dominant group ($p < 0.01$). Age had a significant main effect ($F = 38.75$, partial $\eta^2 = 0.40$, $p < 0.01$). *Post-hoc* tests showed that the IPS of both the IF-dominant and EF-dominant groups was significantly higher among younger individuals than among older individuals under both the IF and EF conditions ($p < 0.01$) (Figure 5). No significant differences in numbers were detected between the IF-dominant and EF-dominant groups when comparing the numbers of participants who performed the IF condition first and those who performed the EF condition first, both in younger ($\chi^2 = 0.78$, $p = 0.38$) and older adults ($\chi^2 = 2.62$, $p = 0.11$).

Comparison of TMT-A times between the groups using 2-way ANOVA showed no significant interaction between the two factors of age and dominance of attentional focus ($F = 2.65$, partial $\eta^2 = 0.04$, $p = 0.11$). Additionally, the age factor had a significant main effect on TMT-A time ($F = 80.30$, partial $\eta^2 = 0.58$, $p < 0.01$). The *post-hoc* test showed that the required TMT-A time was longer in older adults than in younger adults ($p < 0.01$). However, there was no significant main effect of the dominance factor on attentional focus ($F = 1.47$, partial $\eta^2 = 0.03$, $p = 0.23$) (Figure 6).

The relationship between the IPS and TMT-A time in each condition was assessed using Pearson's correlation analysis, which showed that the TMT-A time in younger people was not significantly correlated with IPS under the IF ($r = -0.03$, $p = 0.92$) or EF conditions ($r = -0.08$, $p = 0.78$) in the IF-dominant group and under the IF ($r = -0.35$, $p = 0.20$) or EF ($r = -0.36$, $p = 0.18$) condition in the EF-dominant group (Figure 7). In contrast, in the older IF-dominant group, there was a significant negative correlation between the TMT-A time and IPS under the IF condition ($r = -0.57$, $p = 0.01$) and between the TMT-A time and IPS under the EF condition ($r = -0.60$, $p < 0.01$). However, there was no significant correlation between the IPS and TMT-A time under IF ($r = -0.51$, $p = 0.09$) and EF condition ($r = -0.47$, $p = 0.13$) in the EF-dominant group (Figure 8). Correlation analysis in older adults showed a medium correlation between IPS under the IF and EF conditions and TMT-A time taken in both IF-dominant and EF-dominant groups.

4 Discussion

This study examined the dominance of attentional focus in standing postural control in healthy younger and older adults and the relationship between the dominance of attentional focus and TMT-A time. The results showed that the performance of standing postural control was lower in older adults than in younger adults. However, older adults showed the same attentional focus dominance as did younger adults. Additionally, among older adults, IPS under the IF condition remained stable, regardless of the dominance of attentional focus. However, IPS under the EF condition was notably lower in the IF-dominant group compared with the EF-dominant group. Therefore, it was suggested that performance under the EF condition, which exhibited more variability among individuals than under the IF condition, might have influenced the dominance of attentional focus in older adults. These results suggest that interventions based on attentional focus dominance may enhance standing postural control in older adults. Particularly, in the older IF-dominant group, EF condition interventions decreased standing postural control performance, implying that intervention under the IF condition according to attentional focus dominance may be preferable.

4.1 Effects of attentional focus on standing postural control in younger and older adults

We found that IPS was significantly lower in healthy older adults compared with healthy younger adults. IPS is a standing postural control assessment index that is unlikely to cause a ceiling effect. It has been reported to decline rapidly, particularly after the age of 60 years (Suzuki et al., 2018). In addition, the IPS for 19–25-year-olds and 66–75-year-olds were reported to be 2.08 ± 0.19 and 1.63 ± 0.36, respectively (Suzuki et al., 2018); the results of the present study are similar to those of the aforementioned study. Our finding of a lower IPS among older adults than in younger adults may be attributed to the fact that the ability to control standing posture declines with age (Stoffregen, 2016). Furthermore, IPS has been reported to be heavily influenced by vision and plantar superficial sensation (Suzuki et al., 2018). Visual information processing (Zhang et al., 2008) and plantar sensory processing function (Peters et al., 2016) decline with age. Therefore,

TABLE 1 Comparison of IPS under the IF and EF conditions between younger and older adults.

	IF condition	EF condition	Age × condition		Age		Condition	
			F-value	*P*-value	F-value	*P*-value	F-value	*P*-value
Younger adults	2.18 ± 0.22	2.17 ± 0.21	1.52	0.22	42.64	< 0.01	2.45	0.12
Older adults	1.81 ± 0.29	1.74 ± 0.31						

IPS was significantly higher in younger adults compared with older adults under both IF and EF conditions ($p < 0.05$). IF, internal focus; EF, external focus; IPS, index of postural stability.

it is possible that the IPS in older adults in this study was lower than that in younger adults.

There were no significant differences between the IPS in the younger and older adults under the IF and EF conditions. This result indicates that performance is not necessarily higher under the EF condition than that under the IF condition. Many previous studies have shown that performance is better under the EF condition than under the IF condition (Wulf et al., 2010; Sawai et al., 2022a), and similar results have been reported for postural control (Chiviacowsky et al., 2010). However, we found that there was an individual dominance in the optimal attentional focus condition for standing postural control in healthy younger adults (Sawai et al., 2022b, 2023). This implies that there is an IF-dominant group that performs better under the IF condition and, similarly, an EF-dominant group that performs better under the EF condition. As the optimal attentional focus condition differs between individuals, it is possible that high performance under the EF condition was not observed in this study, as has been reported in many previous studies.

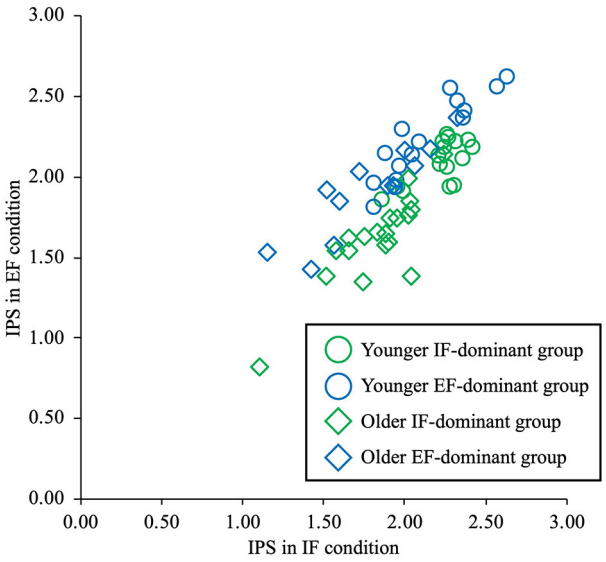

FIGURE 4
The dominance of attentional focus in younger and older adults. The vertical axis shows the IPS values under the EF condition, and the horizontal axis shows the IPS values under the IF condition. The round plots represent data for younger people, and the diamond plots for older adults. The green plot shows the IF-dominant group and the blue plot shows the EF-dominant group. The participants were divided into IF-dominant groups with high IPS under the IF condition and EF-dominant groups with high IPS under the EF condition for both younger and older adults. IPS, index of postural stability; IF, internal focus; EF, external focus.

4.2 The dominance of attentional focus in standing postural control in younger and older adults

The participants in this study were divided into IF-dominant and EF-dominant groups for both healthy younger and older adults. In previous studies, we reported the dominance of attentional focus in standing postural control in healthy younger adults (Sawai et al., 2022b, 2023). The dominance of attentional focus has also been confirmed in an upper limb tracking task in healthy younger adults (Sakurada et al., 2016, 2019a,b, 2022). Therefore, the results of this study indicated that the dominance of attentional focus in standing postural control existed not only in younger adults but also in older adults.

In both the IF-dominant- and EF-dominant groups, the IPS under the IF and EF conditions was lower in older adults than in younger adults. These results indicate that the IPS is affected by age-related decline in the ability to control standing posture, irrespective of the dominance of attentional focus. The ability to control standing posture is reduced in older adults (Stoffregen, 2016), and this is not only due to muscle weakness (Gouveia et al., 2020) but also to a decrease in visual information processing (Zhang et al., 2008) and plantar sensory processing (Peters et al., 2016). Differences in sensory processing characteristics have been reported to exist between the IF-dominant and EF-dominant groups, with superficial sensory processing being prioritized in the IF-dominant group and visual information processing in the EF-dominant group (Sakurada et al., 2022). Both visual information and plantar sensory processing abilities decline with age, which may have led to a lower IPS in older adults than in younger adults in both the IF-dominant and EF-dominant groups. Furthermore, electroencephalography activity in the frontal and parietal lobes is involved in the dominance of attentional focus in standing postural control in young adults (Sawai et al., 2022b). On the other hand, it has been pointed out that older adults had higher electroencephalography activity and mobilize more cortex during postural control than did younger adults (Rubega et al., 2021). This implies that older adults perform effortful postural control by excessive neuronal mobilization. Such changes in neurological strategies for postural control may influence the decreased ability to control standing posture in older adults. Therefore, it is possible that the IPS of the older adults in both the IF-dominant and EF-dominant groups was lower than that of the younger adults in this study as well.

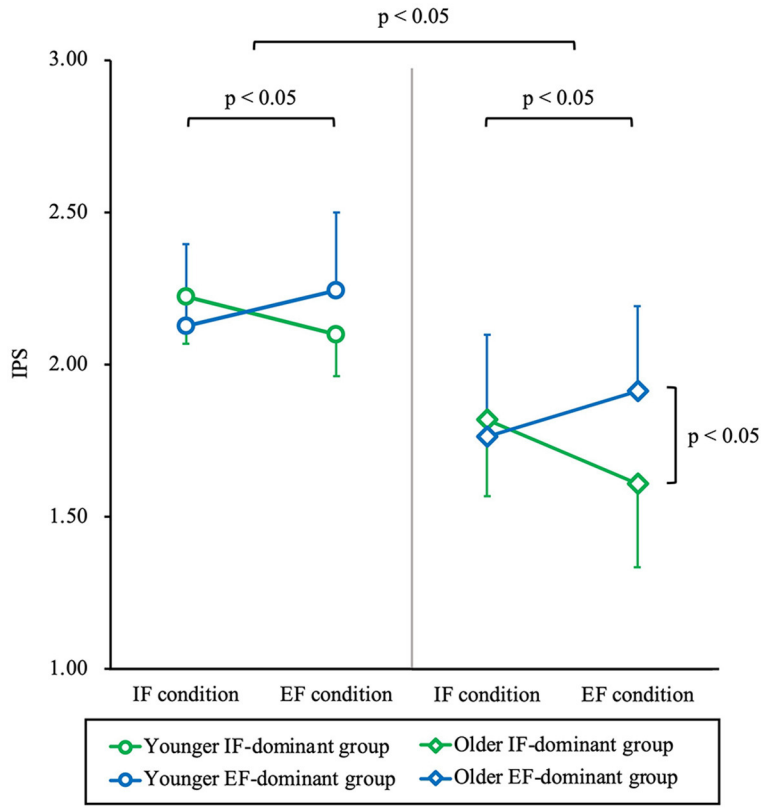

FIGURE 5
Comparison of IPS between younger and older adults, IF-dominant and EF-dominant group, and IF and EF condition. The vertical axis shows IPS. The round plots represent data for younger people, and the diamond plots for older adults. The green plot shows the IF-dominant group and the blue plot shows the EF-dominant group. IPS was significantly lower among the older adults compared to the younger adults ($p < 0.05$). In both younger and older adults, the IF-dominant group had a significantly higher IPS under the IF condition than under the EF condition, and the EF-dominant group had a significantly higher IPS under the EF condition than under the IF condition ($p < 0.05$). Furthermore, IPS under the EF condition was significantly higher in the EF-dominant group than in the IF-dominant group among older adults ($p < 0.05$). IPS, index of postural stability; IF, internal focus; EF, external focus.

4.2.1 The dominance of attentional focus in standing postural control in younger adults

In this study, there was a significant interaction between the factors of condition and dominance of attentional focus. However, there were no significant group differences between the IF-dominant and EF-dominant groups in the IPS under the IF and EF conditions among younger adults. This result indicated that the effect of attentional focus on the IPS might be smaller in the participants with high-standing postural control ability, such as younger adults. In a previous study, it was reported that there was no difference in performance between the IF and EF conditions on easy tasks but that the difference in performance between the IF and EF conditions was more apparent on difficult tasks (Wulf et al., 2007). Thus, attentional focus was found to be more effective in more difficult tasks. It has also been reported that postural control in young adults is carried out by subcortical automatic control and is not affected by the stimuli presented (Honeine et al., 2017). In this study, younger adults had higher standing postural control ability compared with older adults, reducing the difficulty level in the IPS. Therefore, it is possible that the impact of attentional focus on the IPS was small, leading to no significant difference in IPS between the IF-dominant and EF-dominant groups under the IF and EF conditions among younger adults.

4.2.2 The dominance of attentional focus in standing postural control in older adults

Under the IF condition, there were no significant differences in IPS between the IF-dominant and EF-dominant groups in older adults. However, under the EF condition, the IPS was significantly higher in the EF-dominant group than that in the IF-dominant group. This result suggests that performance under the IF condition is independent of the dominance of attentional focus in older adults and that the dominance of attentional focus may influence performance under the EF condition. This means that older adults with a low IPS under the EF condition were in the IF-dominant group, whereas those with a high IPS under the EF condition were in the EF-dominant group.

Compared with younger adults, older adults tend to perform postural control with proprioceptive information that is superior to visual and vestibular sensory information (Wiesmeier et al., 2015). In this study, the participants were asked to focus their attention on their feet under the IF condition, which promotes standing postural control with superficial sensory and proprioceptive superiority (Gottwald et al., 2020). Due to the attention to the proprioceptive senses that older adults tended to use under the IF condition, the IPS under the IF condition may have remained constant, independent of the dominance of attentional focus. Therefore, it

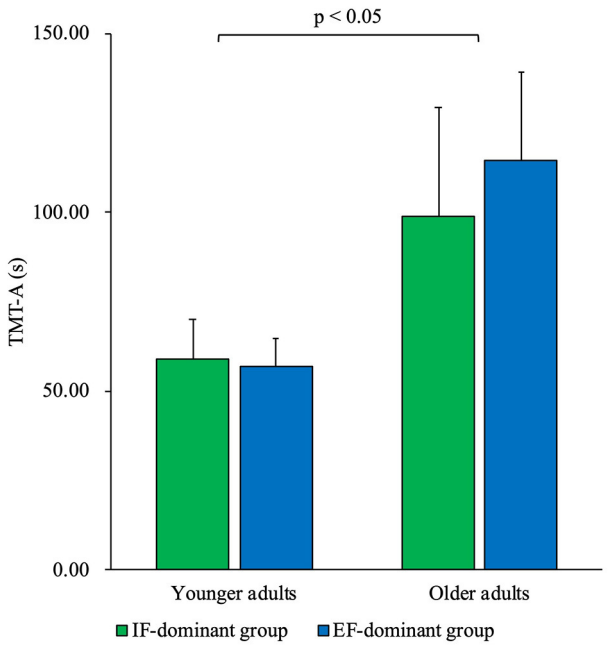

FIGURE 6
The comparison of time required to complete TMT-A between younger and older adults and between IF-dominant and EF-dominant groups. The vertical axis shows the time required for TMT-A. The green bar represents the IF-dominant group, and the blue bar the EF-dominant group. The older adults took significantly longer to complete the TMT-A compared to the younger adults ($p < 0.05$). However, there were no significant differences in the time required to complete the TMT-A between the IF-dominant and EF-dominant groups for both younger and older adults ($p > 0.05$). TMT-A, trail-making test part A; IF, internal focus; EF, external focus.

is possible that there was no significant difference in IPS under the IF condition between the IF-dominant- and EF-dominant groups among older adults.

Visual information processing has been shown to decline with age (Ebaid and Crewther, 2019). Furthermore, there are individual differences in visual information processing in older adults (Owsley, 2012). A correlation between motor perception and postural control in older adults with respect to visual information processing has been reported (Wood et al., 2022). Thus, it is clear that visual information processing, which declines with age, influences postural control. Under the EF condition in this study, attention was focused on the center of gravity on the monitor, which promoted visual information-dominant postural control. Therefore, the finding that the IPS in the IF-dominant group was significantly lower than that in the EF-dominant group under the EF condition among older adults may have been attributed to the individual differences in visual information processing. In conclusion, our results suggested that performance under the EF condition but not under the IF condition could influence the dominance of attentional focus in standing postural control among older adults. On the other hand, it has been reported that in healthy older adults, postural control was not impaired by the presentation of confusing visual information during standing postural control (Pelosin et al., 2018). Thus, the effects of visual information processing on standing postural control in older adults need to be more consistent. Further research is needed to clarify the factors that influence the performance of standing postural control under the EF condition in older adults.

4.3 The relationship between the dominance of attentional focus in standing postural control and attentional function in younger and older adults

The time required for the TMT-A was longer in older adults than in younger adults. However, there was no significant difference between the IF-dominant- and EF-dominant groups. The time required for TMT-A has been reported to increase with age (Hashimoto et al., 2006; Periáñez et al., 2007), and it is possible that the time required for TMT-A was similarly affected by aging in this study, with older adults having a longer TMT-A time compared with younger adults. The TMT-A time may not be a major influencing factor for the dominance of attentional focus, as there were no significant differences between the IF-dominant and EF-dominant groups among either younger or older adults. Previous studies examining the factors associated with the dominance of attentional focus have found that motor imagery characteristics (Sakurada et al., 2019b) and primary somatosensory cortex responses to visual and superficial sensations (Sakurada et al., 2022) are relevant. This suggests that individual characteristics in the processing of sensory-motor information are primarily related to the dominance of attentional focus and that TMT-A time may not be a major associated factor.

The association between IPS under each condition and the time required for TMT-A was examined in each group; no significant correlation was found between IPS and TMT-A time in younger adults. TMT-A is a test of general cognitive and attentional functions, reflecting visual search and scanning abilities and complex attentional functions (Robins Wahlin et al., 1996; Allen and Haderlie, 2010). Cognitive and attentional functions bear no influence on standing postural control in younger adults with high performance compared with older adults (Bernard-Demanze et al., 2009). Therefore, there may have been no association between the TMT-A time and IPS under the IF and EF conditions among younger adults with higher standing postural control performance.

In contrast, among older adults, the IPS in the IF-dominant group under IF and EF conditions showed a significant correlation with TMT-A time. In contrast, the IPS in the EF-dominant group showed no significant correlation with TMT-A time. Considering that the correlation analysis in this study was a subgroup analysis and the number of evaluated participants was small, it can be inferred that the results could be exploratory. Therefore, interpreting the results by focusing on the correlation coefficient rather than on whether a significant correlation was detected is necessary. Based on the above, a medium correlation was found between IPS under the IF and EF conditions and TMT-A in both the older IF-dominant and the older EF-dominant groups. The results indicated that there was an association between standing postural control performance and attentional function in older adults, regardless of attentional focus and the dominance of attentional

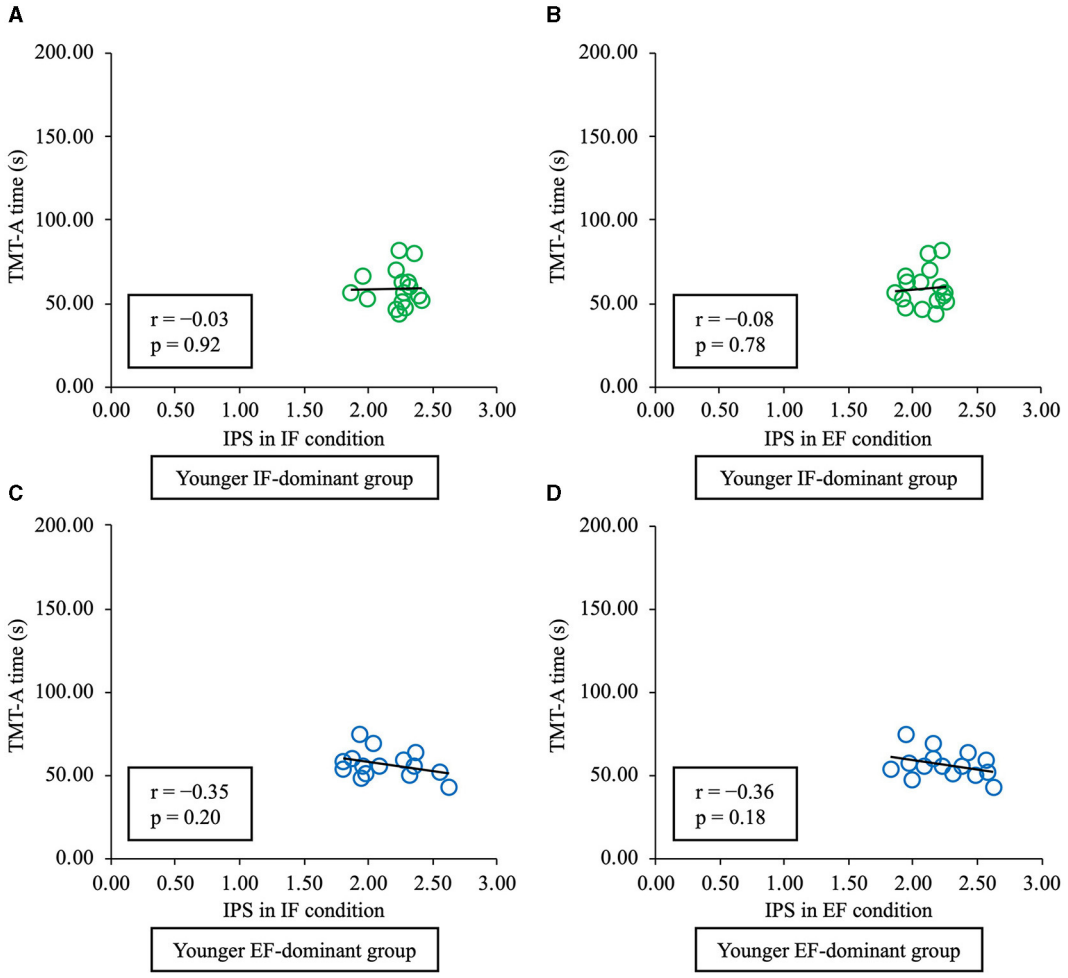

FIGURE 7
The relationship between time required to complete TMT-A and IPS in healthy younger adults. The vertical axis shows the time required for TMT-A, and the horizontal axis shows the IPS for each condition. The green plot represents the IF-dominant group, and the blue plot the EF-dominant group. **(A)** In the IF-dominant group, IPS under the IF condition did not show a significant correlation with TMT-A time ($p > 0.05$). **(B)** In the IF-dominant group, IPS under the EF condition did not show a significant correlation with TMT-A time ($p > 0.05$). **(C)** In the EF-dominant group, IPS under the IF condition did not show a significant correlation with TMT-A time ($p > 0.05$). **(D)** In the EF-dominant group, IPS under the EF condition did not show a significant correlation with TMT-A time ($p > 0.05$). TMT-A, trail-making test part A; IPS, index of postural stability; IF, internal focus; EF, external focus.

focus. The relationship between postural control and attentional function has been verified in many studies. Moreover, it has been reported that older adults could have poorer performance in postural control during dual tasks that required attentional demands (Brown et al., 1999; Woollacott and Shumway-Cook, 2002). In this study, verbal instruction to focus attention on the feet and the center of gravity point was given under each of the IF and EF conditions, and this may have demanded attention. Therefore, a medium correlation may have been found between the TMT-A, which assesses attentional function (Robins Wahlin et al., 1996), and the IPS under the IF and EF conditions.

4.4 Limitations

This study has some limitations. First, it assessed TMT-A time as a relevant factor for the dominance of attentional focus and failed to consider other factors. A previous study on healthy younger participants reported that differences in responses to visual and tactile information in the primary somatosensory cortex were related to the dominance of attentional focus in an upper limb tracking task (Sakurada et al., 2022). Therefore, not only did they validate TMT-A times in their study, but they also demonstrated that other indices may be related to the dominance of attentional focus in standing postural control among older adults. Future studies should examine the factors associated with the dominance of attentional focus from multiple perspectives across many outcomes. Second, although this study examined changes in performance, learning effects could not be examined. Future studies should investigate the effects of attentional focus dominance on motor learning during standing postural control to obtain more clinically useful results. Third, this study failed to take into account the participants' sporting history. A previous study reported that sports history affected the dominance of attentional focus in the upper limb tracking task (Sakurada et al., 2016). Therefore, it is possible that the participants' sporting history also influenced the results of this study. In future studies, assessing the dominance of attentional focus by asking for basic background information

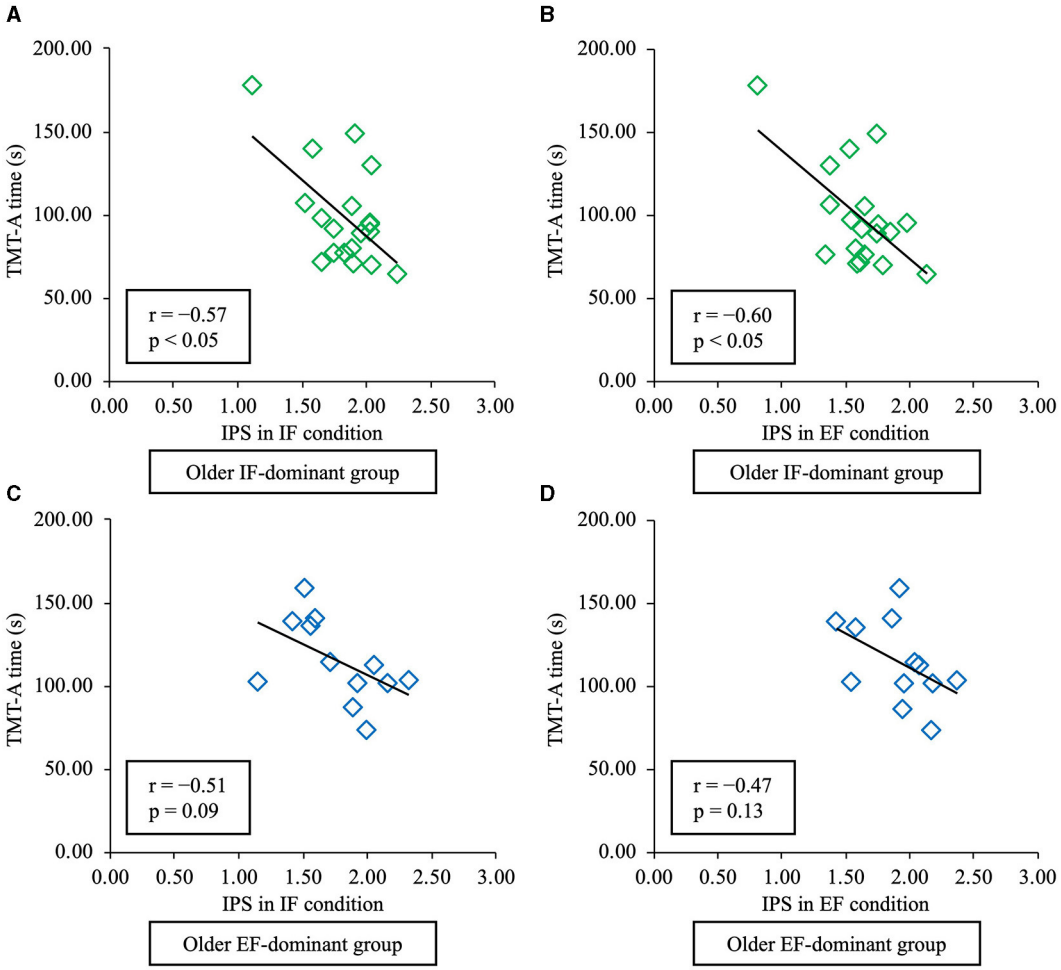

FIGURE 8
Relationship between time required to complete TMT-A and IPS in healthy older adults. The vertical axis shows the time required for TMT-A, and the horizontal axis shows the IPS for each condition. The green plot represents the IF-dominant group, and the blue plot the EF-dominant group. **(A)** In the IF-dominant group, IPS under the IF condition showed a significant negative correlation with TMT-A time ($p < 0.05$). **(B)** In the IF-dominant group, IPS under the EF condition showed a significant negative correlation with TMT-A time ($p < 0.05$). **(C)** In the EF-dominant group, IPS under the IF condition did not show a significant correlation with TMT-A time ($p > 0.05$). **(D)** In the EF-dominant group, IPS under the EF condition did not show a significant correlation with TMT-A time ($p > 0.05$). TMT-A, trail-making test part A; IPS, index of postural stability; IF, internal focus; EF, external focus.

about the participants, such as their sporting history, may be useful. Fourth, the sex ratio of the participants in this study differed between younger and older adults. Although the comparison of the sex ratios showed no significant differences, the differences in the sex ratios may have influenced the results. Future studies could verify the results separately in male and female patients and eliminate the influence of sex to obtain more detailed results. Fifth, in this study, the dominance of attentional focus was examined by performing IPS measures under the IF and EF conditions in a crossover design. A chi-square test showed that the prior condition did not affect the dominance of attentional focus. However, the difference in IPS between the IF and EF conditions was small, and we cannot rule out the possibility that the order in which the task conditions were performed might have affected the dominance of attentional focus. Sixth, in the present study, the IPS under the IF and EF conditions were measured only once each. Therefore, it cannot be definitively determined that the results of the present study are not coincidental and reflect participant characteristics in participants with similar IPS values under the IF and EF conditions. Future research should shed light on the stationarity of the dominance of attentional focus.

4.5 Conclusion

Our results confirmed the dominance of attentional focus in standing postural control in healthy older adults as well as in healthy younger adults. In older adults, the IF-dominant group showed lower standing postural control performance under the EF condition than did the EF-dominant group. These results suggest that the dominance of attentional focus in standing postural control among older adults could influence their performance under the EF condition. They also indicated that standing postural control was affected by attentional function in the IF-dominant group, and this performance was impaired under the EF condition. The results of this study suggest the importance of an individually tailored intervention method based on the dominance of attentional focus for standing postural control among older adults. In particular,

guiding the IF-dominant group toward the IF condition to avoid low performance in standing postural control is important, because the standing postural control of the IF-dominant group tends to diminish under the EF condition. The results of this study might be applied to prevent falls in community-dwelling older adults and to facilitate rehabilitation during hospitalization to effectively improve the standing postural control performance of older adults.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Kyoto Tachibana University Ethics Screening Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. SM: Investigation, Resources, Writing – review & editing. YSa: Investigation, Resources, Validation, Writing – review & editing. SF: Investigation, Validation, Writing – review & editing. RY: Investigation, Validation, Writing – review & editing. YSh: Investigation, Validation, Writing – review & editing. HN: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

YSa is employed by Kissho-Home of Social Welfare Corporation Seiwaen.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy of personalized rTMS to enhance upper limb function in subacute stroke patients: a protocol for a multi-center, randomized controlled study

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Background: Repetitive transcranial magnetic stimulation (rTMS) is widely used therapy to enhance motor deficit in stroke patients. To date, rTMS protocols used in stroke patients are relatively unified. However, as the pathophysiology of stroke is diverse and individual functional deficits are distinctive, more precise application of rTMS is warranted. Therefore, the objective of this study was to determine the effects of personalized protocols of rTMS therapy based on the functional reserve of each stroke patient in subacute phase.

Methods: This study will recruit 120 patients with stroke in subacute phase suffering from the upper extremity motor impairment, from five different hospitals in Korea. The participants will be allocated into three different study conditions based on the functional reserve of each participant, measured by the results of TMS-induced motor evoked potentials (MEPs), and brain MRI with diffusion tensor imaging (DTI) evaluations. The participants of the intervention-group in the three study conditions will receive different protocols of rTMS intervention, a total of 10 sessions for 2 weeks: high-frequency rTMS on ipsilesional primary motor cortex (M1), high-frequency rTMS on ipsilesional ventral premotor cortex, and high-frequency rTMS on contralesional M1. The participants of the control-group in all three study conditions will receive the same rTMS protocol: low-frequency rTMS on contralesional M1. For outcome measures, the following assessments will be performed at baseline (T0), during-intervention (T1), post-intervention (T2), and follow-up (T3) periods: Fugl-Meyer Assessment (FMA), Box-and-block test, Action Research Arm Test, Jebsen-Taylor hand function test, hand grip strength, Functional Ambulatory Category, fractional anisotropy measured by the DTI, and brain network connectivity obtained from MRI. The primary outcome will be the difference of upper limb function, as measured by

FMA from T0 to T2. The secondary outcomes will be the differences of other assessments.

Discussion: This study will determine the effects of applying different protocols of rTMS therapy based on the functional reserve of each patient. In addition, this methodology may prove to be more efficient than conventional rTMS protocols. Therefore, effective personalized application of rTMS to stroke patients can be achieved based on their severity, predicted mechanism of motor recovery, or functional reserves.

Clinical trial registration: https://clinicaltrials.gov/, identifier NCT06270238.

KEYWORDS

stroke, rTMS, functional reserve, neurorehabiliation, personalized medicine

1 Introduction

1.1 Background and rationale

Stroke is still worldwide leading cause of disability, and the global burden has been increasing (1, 2). Impairment of upper limb motor function stands out as the foremost and prevalent sequelae of stroke, significantly impacting stroke patients' independence in activities of daily living (3, 4). Therefore, clinicians are employing various therapies aimed at improving outcomes related to motor function, including conventional rehabilitative physical and occupational therapies.

Transcranial magnetic stimulation (TMS) generates magnetic field to induce electric currents in brain, using a magnetic coil. These currents primarily stimulate axons of the neural circuits and enable to assess motor cortex function or corticospinal connectivity (5). By recording motor evoked potentials (MEPs) in distal muscles following TMS, disease-related changes in corticospinal output can be assessed. Therefore, TMS has been proven useful as a predictor of motor recovery in stroke patients using measures such as motor threshold, amplitude and latency of MEP, cortical silent period, or central motor conduction time (5, 6). Since the early 2000s, the use of repetitive transcranial magnetic stimulation (rTMS) has emerged and is now widely utilized to enhance upper limb function in stroke patients, due to its feasibility, non-invasive nature and painless application (7–10). The underlying patho-mechanisms in applying rTMS therapy was mainly based on the neuroplasticity and the interhemispheric competition model theory (11–14). Applying rTMS to human cortex has been proven to modulate cortical excitability, leading to recovery or reorganization of the functional connectivity (5, 15). The neuroplasticity, in the context of stroke, is thought as the brain's capacity to modulate its activity in response to stimuli, thereby compensating for damages resulting from stroke (16). rTMS therapy targets this plasticity by either inhibiting or exciting neural activity to induce or restore the desired plasticity in the brain (17, 18). In stroke patients in the acute phase, it is known that along with functional loss in the ipsilesional hemisphere, there are alterations in the interaction between the ipsilesional hemisphere and the contralesional hemisphere via the corpus callosum (19). It is thought that in regions remote from the brain lesion, there may be changes in neuroanatomy and cortical activity in both cerebral hemispheres (20). As a result, bilateral activation of both primary motor cortices is observed during movement in post-stroke patients, resulting in poor motor function compared to healthy people (21). Based on these theories, in stroke patients, many previous studies have demonstrated the effect of inhibitory low-frequency rTMS or continuous theta burst stimulation (cTBS) applied at contralesional primary motor cortex (M1) and facilitatory high-frequency rTMS or intermittent theta burst stimulation (iTBS) applied at ipsilesional M1 in enhancing upper limb function (22, 23).

The currently well-known conventional rTMS protocols for stroke patients involve applying inhibitory rTMS at the contralesional M1 or facilitatory rTMS at the ipsilesional M1. However, some studies demonstrated that these conventional rTMS protocols showed no significant effects when applied to severe hemiplegic stroke patients (24, 25). These results may imply that cortical activity or neural plasticity of individual stroke patients is not unified. Also, in cases where ipsilesional motor pathways are severely damaged, stimulating M1 may not be the optimized therapy for enhancing upper limb motor recovery. In fact, some previous studies have investigated the ipsilesional premotor cortex (PM) or supplementary motor area (SMA), and contralesional PM may replace the function of the damaged ipsilesional M1, although no consensus has been reached yet (26–29). Schulz et al. demonstrated a significant interaction between the corticospinal tract (CST) and corticocortical connections, implying that the ipsilesional ventral PM plays a role in patients with significant damage in CST (30). Sankarasubramanian et al. (31) also reported that the contralesional dorsal PM may support recovery in patients who have experienced extensive damage to ipsilesional motor pathways. In addition, Di Pino et al. (32) suggested a bimodal balance recovery model over the interhemispheric competition model. They suggested that interhemispheric balancing should be considered along with the functional reserve spared by every patient in the recovery model, not in isolation. Given the diverse underlying pathophysiology and recovery processes within stroke, this suggestion appeared reasonable. In 2018, Harvey et al. (33) demonstrated that applying inhibitory rTMS at ipsilesional M1 did not show effectiveness. Following the release of this trial, increasing inquiries have emerged regarding the rationality of applying conventional rTMS protocols based on the interhemispheric competition model. Ultimately, it is believed that employing a conventional rTMS approach, which applies the same protocol to everyone without considering individual characteristics,

has limitations. Therefore, a consideration of individual functional reserve will be necessary for the implementation of rTMS tailored to each individual.

Besides the stimulating target of rTMS, another important consideration when applying rTMS therapy is the accuracy of the stimulation. The conventional rTMS treatment approach has historically positioned the area of maximal magnitude of the electric field induced by TMS along the central axis of the stimulation coil. Stimulation was conducted by aligning the coil to ensure that the central axis of the coil passed through the stimulation area. Additionally, determining the stimulation area was achieved by identifying the location that elicited the largest transcranial magnetic stimulation-induced motor-evoked potentials (TMS-induced MEPs), requiring numerous attempts of TMS to accurately ascertain the stimulation site (34). In addition, protocols based on anatomical landmarks or the 10–20 system have been used to stimulate non-motor areas where TMS-induced MEPs are not measured, which may increase the imprecision of rTMS targeting (35). Recently, a neuronavigation system is considered a viable method for obtaining accurate stimulation targets. However, a critical limitation of employing the neuronavigation is its expense, making it difficult to utilize in general environments (36). Recent advancements in neuroimaging techniques have enabled the development of computational brain modeling and electric field simulation techniques based on brain images such as magnetic resonance imaging (MRI) obtained from patients, which can address the limitations of conventional rTMS targeting methods (37, 38). Specifically, through the prediction and analysis of electric fields reflecting the unique anatomical information of the patient's brain based on MRI, it has been revealed that the area of maximum magnitude of the electric field does not necessarily align with the central axis of the coil due to variations in brain structure (39, 40). Moreover, simulations have shown that when stimulating areas are targeted to achieve maximum field strength, actual TMS-induced MEPs are increased (41). Therefore, it is imperative to utilize electric field simulations and optimization processes based on brain imaging obtained from patients to determine the position and orientation of the TMS coil that will generate the optimal stimulation for the given target stimulation area. This approach should be applied to rTMS therapy to ensure its effectiveness.

Therefore, the aim of this study is to demonstrate the efficacy of rTMS protocols based on the functional reserve of individual stroke patients, including exploring the accurate stimulating target. We anticipate that our study protocols will demonstrate superiority over the conventional inhibitory rTMS protocol applied to the contralesional M1. Additionally, by utilizing the MRI of each individual patient, we aim to achieve accurate stimulation targets without relying on the neuronavigation, thereby offering convenience and cost-effectiveness for broader use. In addition, we would like to explore the mechanisms of personalized rTMS by performing serial resting-state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI).

2 Methods and analysis

2.1 Study setting

This is a prospective, single-blind with blind observer, parallel-group design, multi-center, randomized controlled clinical trial. This study will recruit 120 patients with stroke in the subacute phase who are suffering from the upper extremity motor impairment, from five different hospitals in Korea. Participating hospitals are Samsung Medical Center, Seoul; Seoul National University Hospital, Seoul; Bucheon St. Mary's Hospital, The Catholic University of Korea, Seoul; St. Vincent's Hospital, The Catholic University of Korea, Seoul; Yongin Severance Hospital, Yongin.

The participants will be allocated into three different study conditions according to their functional reserve, as follows: Study condition (1) participants with preserved ipsilesional CST, confirmed by response of TMS-induced MEPs, Study condition (2) participants with no response of TMS-induced MEPs, but with preserved ipsilesional PM cortex and ipsilesional CST confirmed by DTI, and Study condition (3) participants with no preservation of ipsilesional CST. After the allocation, participants will be randomly assigned to the intervention-group or control-group of each study condition through randomization. The participants of the intervention-group in the three study conditions will receive different protocols of rTMS intervention: Study condition (1) high-frequency rTMS on ipsilesional M1, Study condition (2) high-frequency rTMS on ipsilesional ventral PM, and Study condition (3) high-frequency rTMS on contralesional M1. The participants of the control-group in all three study conditions will receive the same rTMS protocol: low-frequency rTMS on contralesional M1. A schematic diagram is shown in Figure 1.

Evaluations to assess the functional reserve and motor function will be conducted as follows: (1) at baseline (T0), (2) after 1 week, following 5 sessions of rTMS intervention [during-intervention (T1)], (3) at the end of the rTMS intervention [post-intervention (T2)], and (4) 2 months after the end of the intervention [follow-up (T3)]. The specific timeline of participants is shown in Table 1.

2.2 Eligibility criteria

The inclusion criteria for this study are as follows: (1) hemiplegic stroke (ischemic or hemorrhagic stroke with corresponding lesion determined by MRI or computed tomography scan) patients in the subacute phase (7 days to 3 months from the onset) who are currently hospitalized, (2) Fugl-Meyer Assessment (FMA) score of the upper extremity ≤42, (3) adequate language and cognitive function to perform at least a 1-step obey-command, (4) pre-stroke functional level of modified Rankin Scale (mRS) ≤1, (5) aged ≥19 years old, and (6) patients willing to sign the informed consent. The exclusion criteria are as follows: (1) patients with transient ischemic attack, defined as a rapid-onset focal neurological deficit lasting less than 24 h (42) (2) those with contraindications to rTMS, such as epilepsy, implanted metal objects in the head, or a history of craniotomy, (3) those with progressive of hemodynamically unstable medical conditions, (4) those with coexisting neurological conditions, such as spinal cord injury or Parkinson's disease, (5) those with major psychiatric disorders, such as major depression, schizophrenia, or dementia, (6) those having contraindications to conduct an MRI study, (7) those who are pregnant or lactating, and (8) patients who have refused to participate in this study.

2.3 Allocation

The 120 eligible participants will be allocated into three study conditions based on the functional reserve of each participant,

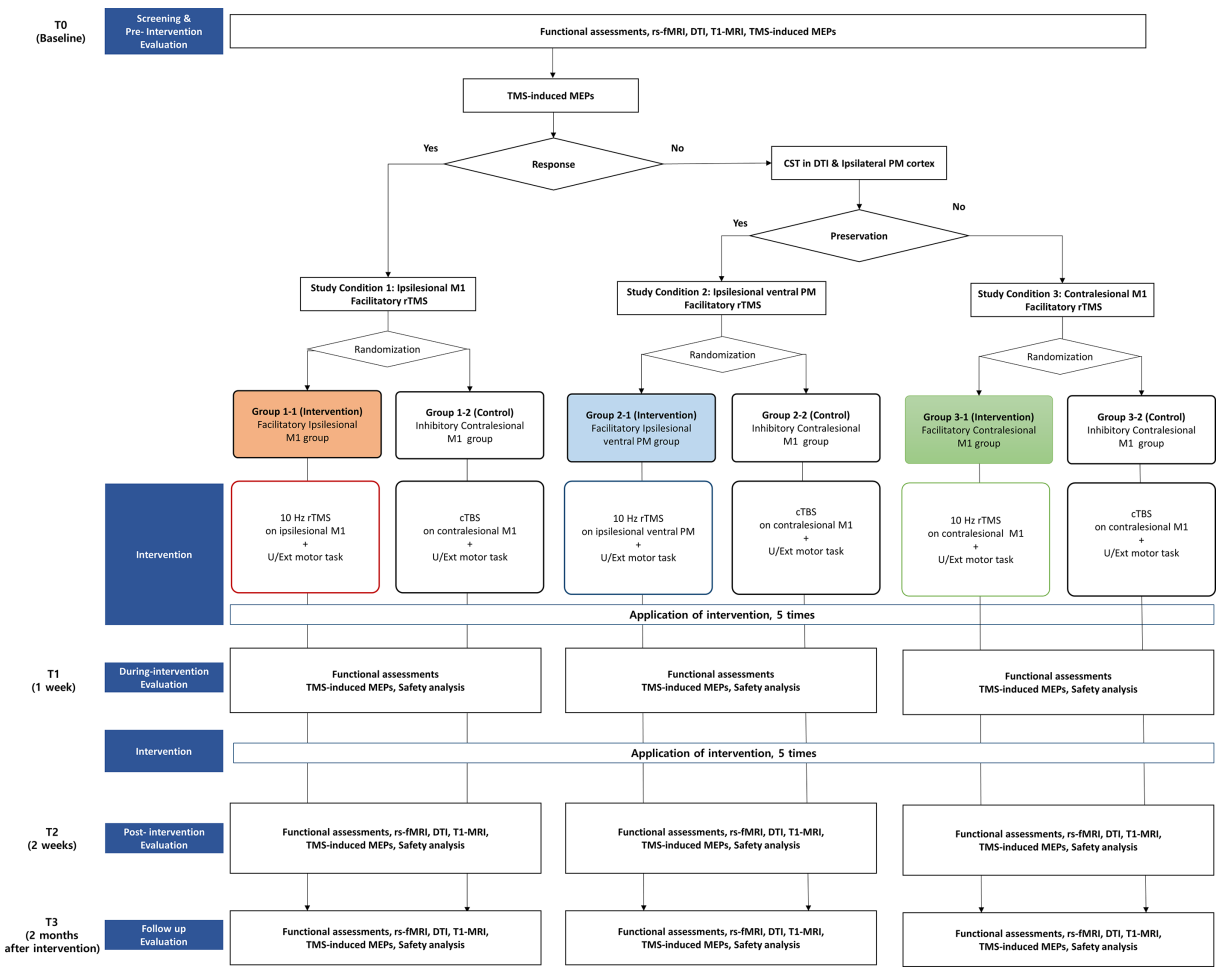

FIGURE 1
Design and flowchart of the study.

measured by the results of the brain MRI, TMS-induced MEPs, and DTI evaluations. Each condition will consist of 40 patients and they will be randomly allocated into the intervention-group and control-group in a 1:1 ratio. The allocation will be performed by the one researcher of each participating hospital, who will be responsible for the randomization, will not have contact with the participant, and will not be involved in data collection or analysis. The randomization will be done by using a randomization table generated by the www.randomization.com. The randomization sequence will be concealed and only the research principal investigator (PI) will have access authority.

2.4 Blinding

The participants and assessors will be blinded, not be aware of the group allocation. Statistical analysis will also be conducted by data analysts without awareness of the group allocation. Only clinicians applying rTMS intervention will not be blinded, as they will apply rTMS over different stimulation sites based on the protocols. Blinding will be continued until the end of the study, including data analysis.

2.5 Intervention

The rTMS intervention will utilize either the Magstim Rapid^2 (Magstim Co. Ltd., United Kingdom), or the MagPro X100 (MagVenture, based in Lucerne Marken, Denmark), employing the 70-mm figure-of-eight coil. The intervention will be applied as high-frequency protocols to the participants in the intervention-group in all three study conditions: 20 sessions of 10-Hz rTMS, 50 pulses per session with a 25-s interval between sessions, totaling 1,000 pulses (43). The difference among the three study conditions will be the targeted stimulation sites based on the functional reserve and stimulating intensity, as follows: (1) ipsilesional M1 and intensity set at 90% of the resting motor threshold (rMT) measured at contralateral first dorsal interosseous muscle (FDI) following stimulation of ipsilesional M1 for Group-1, (2) ipsilesional ventral PM and intensity set at 90% of the rMT measured at contralateral FDI following stimulation of contralesional M1 for Group-2, (3) contralesional M1 and intensity set at 90% of the rMT measured at contralateral FDI following stimulation of contralesional M1 for Group-3. The control-group of all three study conditions will be applied the same cTBS protocol for rTMS on contralesional M1, as follows: TMS pulses will

TABLE 1 Timeline of enrolment, interventions, and assessments of this study.

	Enrolment	Baseline	Intervention (1 ~ 5)	During-intervention	Intervention (6 ~ 10)	Post-intervention	Follow-up
Timepoint		*T0*		*T1*		*T2*	*T3*
Informed consent	O						
Eligibility screen	O						
Allocation		O					
Assessments							
rs-fMRI		O				O	O
DTI		O				O	O
T1-MRI		O				O	O
TMS-induced MEPs		O		O		O	O
FMA		O		O		O	O
Box and block test		O		O		O	O
ARAT		O		O		O	O
Jebsen-Taylor hand function test		O		O		O	O
Hand grip strength test		O		O		O	O
FAC		O		O		O	O
Adverse events			O	O	O	O	O
Application of intervention							
Intervention			O		O		

rs-fMRI, resting-state functional MRI; T1-MRI, T1-weighted structural images of brain MRI; TMS-induced MEPs, transcranial magnetic stimulation induced motor evoked potentials; FMA, Fugl-Meyer Assessment; ARAT, Action Research Arm Test; FAC, Functional Ambulation Category.

be delivered as a 3-pulse burst at 50 Hz applied at 5 Hz for 40 s, with a stimulating intensity set at 70% of the rMT measured at contralateral FDI following stimulation of contralesional M1, totaling 600 pulses (44, 45). All participants will receive rTMS intervention once a day, 5 days per week, for 2 weeks, totaling 10 sessions of rTMS intervention.

The selection of the target stimulation site, specifically the ventral PM, will be manually identified using anatomical landmarks by an expert in neuroanatomy. Following the identification of the ventral PM, the Neurophet tES LAB software (NEUROPHET Inc., Seoul, Republic of Korea) will be employed. This software processes each participant's T1-weighted brain images, which are acquired during the pre-intervention evaluation. The software then reconstructs these images into a three-dimensional model of the brain. Based on this model, the software provides guidance for the precise placement of the stimulation coil on the skin. The stimulating target of M1 will be identified using TMS-induced MEPs, where the maximum peak-to-peak amplitude in the contralateral FDI muscle is achieved (45, 46).

In addition, all participants will receive inpatient conventional rehabilitation therapy, consisting of occupational and physical therapy for 30 min each, twice daily, for 2 weeks, as well as the routine pharmacotherapy based on the guidelines for management of stroke patients (47–49).

During the intervention, participants are allowed to withdraw based on the following criteria: (1) those willing to withdraw, (2) loss to follow-up, (3) occurrence of adverse events, following withdrawal requests from participants, (4) other reasons deemed unsuitable for the progress of the study by the researchers.

3 Data collection

3.1 Brain imaging and cortical excitability

Brain imaging data, comprising rs-fMRI, DTI, and T1-weighted structural images, will be obtained using 3-T scanners (Philips Ingenia CX, Philips Elition, Siemens Magnetom Trio, Siemens Magnetom Vida). The rs-fMRI will be employed to extract brain networks through functional connectivity analysis. Alterations in brain network properties resulting from the intervention will be investigated by analyzing connectivity strength, employing graph theory, and conducting comprehensive assessments of both global and local networks, as well as intra- and inter-hemispheric networks (50). During the resting-state scan, participants will be directed to close their eyes and maintain stillness. Each session will involve the collection of 180 whole-brain images, utilizing the following metrics: 75 axial slices, slice thickness = 2 mm, no gap, matrix size = 112 × 112 or 124 × 124, and repetition time = 2000 ms. DTI will be utilized to extract the integrity of major neural pathways and structural networks through fiber tractography (51). It will also be used to investigate changes in the characteristics of integrity and networks resulting from the intervention (52). Each session will acquire more than 30 diffusion-weighted images with b = 1,000 s/mm2, ensuring a minimum of 75 axial slices, slice thickness = 2 mm, no gap, and matrix size = 112 × 112 or 128 × 128. Fractional anisotropy values (FA) of posterior limb of internal capsule (PLIC), and reconstructed corticospinal and corticobulbar tract will be obtained (53, 54). T1-weighted structural images will be used to ascertain the individual

target positions of the ventral PM. These images will be acquired with a resolution and slice thickness of 1 mm or less to accurately guide the position of the TMS coil.

The cortical excitability of each participant will be measured, using the TMS-induced MEPs. TMS-induced MEPs will be assessed by single magnetic stimulations at 120% of the rMT over the M1 using a 70-mm figure-of-eight coil. During the experiments, participants will sit comfortably in an armchair with their eyes open. A Synergy electromyography/evoked potentials system (Medelec Co. Ltd., Kingswood, Bristol, United Kingdom) will be used to record and monitor the activity of the contralateral FDI muscle following stimulating over the M1 using single-pulse TMS. TMS will be applied using a BiStim^2 stimulator (Magstim Co. Ltd., Spring Gardens, Whitland, Carmarthenshire, Wales, United Kingdom) equipped with a 70-mm figure-of-eight coil. The coil would be held tangentially to the scalp, with the handle pointing backward and laterally at 45° from the mid-sagittal line. Using TMS, the optimum position ("the hot spot") will be defined as the site where TMS-induced MEPs of maximum peak-to-peak amplitude in the contralateral FDI muscle. We will define the rMT as stimulus percentage of maximal stimulator output (MSO) that elicits a minimum peak-to-peak amplitude of MEP over 50uV in at least 5 out of 10 trials (5). This rMT data will be used for determining the intensity of the rTMS intervention in this study. Including the aforementioned rMT, amplitude and latency of MEP will be recorded as TMS-induced MEPs data. To measure the amplitude and latency, the intensity of the TMS stimulation will be set at 120% of the measured rMT. The stimulation will be repeated 10 times, with intervals of 5 s or more. The average peak-to-peak amplitude and latency of the top 5 responses will be measured and recorded (55). The latency will be the time between the onset of the TMS stimuli and the onset action potential (56). In addition, medications known to have potential effects on MT or MEP and the risk of seizures associated with rTMS will also be documented (15, 57).

3.2 Functional assessment

Functional assessments will be conducted at T0, T1, T2, and T3 periods in each participating hospital. To maintain the data quality and inter-rater reliability, the assessors will be trained before the start of the study and uniform manuals will be shared with the assessors and research investigators. In this study, all functional assessment tools selected are widely used for stroke patients and have been frequently employed in previous studies using rTMS (22, 23). Additionally, their reliability and validity have been proven. For motor function, FMA will be used. FMA measures the movement, reflexes, coordination, and speed of limbs (58, 59). The total, upper extremity (UL), and lower extremity (LL) score of FMA will be assessed separately. For hand function assessments, the following tests will be used: the Box and Block Test, reflecting clinical manual dexterity (60, 61); the Action Research Arm Test (ARAT), measuring gross motor skills, grasp., grip, and pinch (62); the Jebsen-Taylor Hand Function Test, assessing the fine motor function of the hand used in daily activities (63, 64); and the Hand Grip Strength Test (65). The Functional Ambulation Category (FAC) will be used to assess ambulatory function, categorizing patients by their level of dependence in walking (66).

3.3 Outcomes

The primary outcome of this study is difference of FMA-UL from baseline (T0) to post-intervention (T2). The secondary outcomes of this study are as follows:

(1) Differences of FMA-total, FMA-UL, FMA-LL, Box and block test, FAC, ARAT, Jebsen-Taylor hand function test, hand grip strength test from baseline (T0) to during-intervention (T1).
(2) Differences of FMA-total, FMA-LL, Box and block test, FAC, ARAT, Jebsen-Taylor hand function test, and hand grip strength test, FA of PLIC, FA of reconstructed corticospinal and corticobulbar tract, global and local connectivity obtained from rs-fMRI from baseline (T0) to post-intervention (T2).
(3) Differences of FMA-total, FMA-UL, FMA-LL, Box and block test, FAC, ARAT, Jebsen-Taylor hand function test, and hand grip strength test, FA of PLIC, FA of reconstructed corticospinal and corticobulbar tract, global and local connectivity obtained from rs-fMRI from baseline (T0) to follow-up (T3).

3.4 Sample size, recruitment

Based on the primary outcome of this study and previous literature, we have established the study's power (1-β) at 80% and a significance level (α) of 5%. The clinically significant effect size (δ) has been designated as 7.25, with an expected standard deviation (σ) of 7.70 (67, 68). Sample size calculation was conducted using Lehr's formula, with an expected follow-up rate of 90% (68, 69). Finally, the calculated sample size was 120, with each subgroup consisting of 40 participants.

Recruitment of the study participants will be conducted by each participating hospital.

Every research investigator will recruit participants from each hospital who are eligible to participate in the study. Participants will be informed about the current treatment guidelines regarding upper extremity dysfunction in stroke patients, as well as the potential and adverse effects of this study.

3.5 Statistical methods

Demographic and clinical characteristics were reported in terms of frequencies and percentages for categorical variables, while means and standard deviations (SD) were utilized for numerical variables. To compare baseline characteristics of the intervention and control group, an independent t-test and the Wilcoxon Signed-rank test will be used for normally distributed and non-normally distributed variables, respectively. The normality of each variable will be examined using the Shapiro–Wilk test.

All participants undergoing intervention in this study will be included in the intention-to-treat (ITT) set. Safety analyses will be conducted based on the ITT set. Participants who completed all of the evaluation regarding the study protocol will be classified as per-protocol (PP) set. The efficacy analyses will be conducted based on the ITT set. For missing values, data will be analyzed using the Last Observation Carried Forward (LOCF) method. Efficacy analyses well

be conducted on the primary and secondary outcomes. For outcome variables, the normality will be examined using the Shapiro–Wilk test. If variables demonstrate normal distribution, a repeated measures analysis of variance (RM-ANOVA) will be used to evaluate the effect of time and groups, including the interaction. If non-normality is found, the Friedman test will be used to determine the differences between the groups. During the analyses, baseline characteristics will be used as covariates for adjustment. In addition, independent t-test or Wilcoxon Signed-rank test will be used to compare parameters between the intervention group and the control group in each condition. Statistical significance will be set at a p-value <0.05 for all the analyses.

3.6 Data management and monitoring

All data will be collected using standardized electronic Case Report Form (eCRF) and study participants will be identified only by a research-specific serial number. All personal information and collected data of participants will be maintained in confidentiality under the responsibility of research PI of each participating hospital. All personal information and collected data of participants will be maintained in confidentiality under the responsibility of the research PI of each participating hospital. They will be stored in password-protected files and kept in a locked facility. Routine supervision of the data will be conducted by one of researchers in each participating hospital, independent of other research investigators. Data analysis will be conducted by data analysts, independent of other research investigators. PIs will meet every month to review the implementation of this study. There are no conflicts of interest among all participating researchers.

3.7 Adverse events

Adverse events expected in this study include discomfort, dizziness, nausea, headache, hearing disturbance, pruritus, allergic reaction, or localized pain, as described in previous studies. The most serious expected side effect if a seizure; however, the occurrence of seizure is rarely reported (14, 22). All adverse events will be monitored. All adverse events that occurred will be reported to research principal investigators, ethics committee of each participating hospital, and the Ministry of Food and Drug Safety of the Republic of Korea within 7 days.

4 Discussion

The objective of this study was to determine the effects of protocols of rTMS therapy based on the functional reserve of each hemiplegic stroke patient in subacute phase, compared to conventional low-frequency rTMS therapy on contralesional M1. To the best of our knowledge, this is the first study willing to determine the effects of applying different protocols of rTMS therapy based on the functional reserve of each patient.

From this study, we anticipate several advantages distinct from those of previous studies. Firstly, this approach could be more effective compared to unified conventional rTMS protocols applied to stroke patients regardless of their severity. The main purpose of this study protocol is to validate a strategy based on a predicted mechanism of motor recovery, defined as functional reserves, that can overcome the limitations of conventional rTMS methods. Although the concept of functional reserves in stroke patients has been proposed, there is a lack of research on the application of stroke rehabilitation strategies using functional reserves (16, 70, 71). If successful, this study is expected to serve as a basis for the application of new rehabilitation strategies utilizing functional reserves, in addition to suggesting a new personalized approach to the application of rTMS in stroke patients.

Secondly, instead of relying on the expensive neuronavigation system, we intend to select accurate stimulation targets based on the MRI of each individual stroke patient. By reducing the economic expense while maintaining accuracy in rTMS therapy, this protocol method could be more conveniently utilized in various situations, facilitating further treatment and research. In particular, it is expected to provide an effective strategy that can be applied to rTMS targeting methods where it is difficult to determine the stimulation location with TMS-induced MEPs, such as the PM, SMA, dorsolateral prefrontal cortex, and cerebellum.

Lastly, by combining the analysis of serial MRI and DTI evaluations with the results of the personalized rTMS protocols in this study, we expect to approach the underlying mechanisms of rTMS therapy in enhancing upper limb motor recovery in stroke patients. The practical validation of functional reserves and the results on neurophysiological mechanisms of personalized rTMS are expected to serve as a basis for future studies on the improvement of upper limb function in stroke patients.

Ethics and dissemination

The PI of the Samsung Medical Center will be the Chief Investigator (CI) of this study. The CI will inform the other PIs of each participating hospital regarding important protocol amendments. The CI will report these amendments to the Ministry of Food and Drug Safety of the Republic of Korea. The PI of each participating hospital will report these amendments to their respective ethics committee and research teams.

Prior to inclusion of participants, all participating hospitals obtained institutional review board (IRB) approval for this study (Samsung Medical Center, 2023–11-164; Seoul National University Hospital, 2,312–167-1498; Bucheon St. Mary's Hospital and St. Vincent's Hospital, The Catholic University of Korea, XC24DND30004; Yongin Severance Hospital, 9–2024-0013). If any protocol modifications are needed, further approval from the IRB will be obtained from all participating hospitals. Informed consent will be obtained from all participants prior to their inclusion in this study by research investigators. In addition, this study has been registered in the clinicaltrials.gov (NCT06270238). The results of this study are expected to be published within 2 years of its completion.

Author contributions

HL: Investigation, Writing – original draft, Methodology. DHK: Project administration, Conceptualization, Writing – review & editing, Supervision. HS: Project administration, Conceptualization, Writing – review & editing, Supervision. SI: Project administration, Writing – review & editing, Supervision, Conceptualization. YY: Writing – review & editing, Investigation, Methodology. NK:

Project administration, Writing – review & editing, Conceptualization, Supervision. JL: Project administration, Writing – review & editing, Supervision, Conceptualization. DK: Project administration, Writing – review & editing, Supervision, Conceptualization. H-YP: Writing – review & editing, Investigation, Methodology. M-JY: Writing – review & editing, Methodology, Investigation. YK: Writing – review & editing, Methodology, Investigation. HK: Writing – review & editing, Methodology, Investigation. WC: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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Conflict of interest

DK was employed by NEUROPHET Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Theoretical proposal for restoration of hand motor function based on plasticity of motor-cortical interhemispheric interaction and its developmental rule

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After stroke, the poorer recovery of motor function of upper extremities compared to other body parts is a longstanding problem. Based on our recent functional MRI evidence on healthy volunteers, this perspective paper proposes systematic hand motor rehabilitation utilizing the plasticity of interhemispheric interaction between motor cortices and following its developmental rule. We first discuss the effectiveness of proprioceptive intervention on the paralyzed (immobile) hand synchronized with voluntary movement of the intact hand to induce muscle activity in the paretic hand. In healthy participants, we show that this bilateral proprioceptive-motor coupling intervention activates the bilateral motor cortices (= bilaterally active mode), facilitates interhemispheric motor-cortical functional connectivity, and augments muscle activity of the passively-moved hand. Next, we propose training both hands to perform different movements, which would be effective for stroke patients who becomes able to manage to move the paretic hand. This bilaterally different movement training may guide the motor cortices into left–right independent mode to improve interhemispheric inhibition and hand dexterity, because we have shown in healthy older adults that this training reactivates motor-cortical interhemispheric inhibition (= left–right independent mode) declined with age, and can improve hand dexterity. Transition of both motor cortices from the bilaterally active mode to the left–right independent mode is a developmental rule of hand motor function and a common feature of motor function recovery after stroke. Hence, incorporating the brain's inherent capacity for spontaneous recovery and adhering to developmental principles may be crucial considerations in designing effective rehabilitation strategies.

KEYWORDS

motor cortex, interhemispheric interaction, fMRI, EMG, neurorehabilitation, development, hand motor function, proprioception

1 Introduction

The poorer recovery of motor function of upper extremities after stroke compared to other body parts is a longstanding problem (1). This perspective paper proposes systematic hand motor rehabilitation utilizing the plasticity of interhemispheric interaction between the motor cortices and following its developmental rule, based on recent neuroscientific evidence.

1.1 Motor-cortical activity after stroke

The motor cortex (precentral gyrus), which includes the primary motor cortex (M1) and dorsal premotor cortex (PMD), is the executive locus of motor control; damage to this area or descending tracts from this area can cause severe motor paralysis of the limbs. However, brain plasticity allows for functional recovery even in adult brains (2, 3). Interestingly, this functional recovery does not occur randomly. For example, when a patient manages to move a paretic hand after stroke, the contralesional motor cortex ipsilateral to the hand is often recruited in addition to the ipsilesional one, so that bilateral activity can be observed (2, 4). This bilaterally active mode is a spontaneous brain reaction observed relatively early after stroke (within 10 days), and can be considered a state whereby the brain is searching for a new motor control pathway (including a pathway from the ipsilateral motor cortex) by trial and error to move the paretic hand. In other words, this bilateral mode is the first step toward restoring motor function (2). Recent animal studies have suggested that this bilaterally active mode is caused by disinhibition of interhemispheric inhibition between the left and right motor cortices (5) by acetylcholine modulating GABAergic interneurons (6).

1.2 Motor-cortical activity in healthy adults

In the brain of typically developed young adults, there are interhemispheric facilitatory and inhibitory circuits between the two motor cortices (7). When young adults perform simple unilateral movements (e.g., simple button pressing with a finger or simple hand alternating extension-flexion movements), the contralateral motor cortex is usually activated, while the ipsilateral motor cortex is inhibited (8–11), probably due to interhemispheric inhibition between the two motor cortices (12). On the other hand, when young adults perform complex unilateral movements (e.g., stick-spinning or ball rotation with multiple fingers), there is activity in the ipsilateral motor cortex (especially in the PMD) in addition to the contralateral activity (8, 13, 14). Thus, the human brain adaptively controls movement by flexibly and plastically altering interhemispheric inhibition between the two motor cortices.

1.3 Developmental of motor-cortical interhemispheric inhibition

The interhemispheric inhibition is not innate. During childhood, interhemispheric inhibition between the left and right motor cortices is still immature, maturing during adolescence (9, 10, 15). Hence, the motor cortex before adolescence is in a bilaterally active mode, but this begins to change in adolescence to a left–right independent mode that allows the left and right hands to move independently. On the other hand, interhemispheric interaction between the two motor cortices can be greatly affected by training. We have recently shown that a top wheelchair racing Paralympian who trained from school age for special training in wheelchair racing, which requires bimanually synchronized upper-limb movements, shows a bilaterally active mode even in adulthood. She showed bilateral motor-cortical activations even during a simple alternating extension-flexion movement of the right hand, which should be called hyper-adaptation phenomenon rarely seen in typically-developed people (11). This finding inspired an intervention using bimanually synchronized movements that can act on the plasticity of interhemispheric interaction between the two motor cortices.

In this paper, we first propose the effectiveness of an intervention to facilitate the motor cortices into bilaterally active mode, i.e., passive movement of one hand synchronized with voluntary movement of the other hand, based on our recent findings in healthy younger adults (Section 2). Next, we propose the effectiveness of training both hands to perform different movements to guide the motor cortices into left–right independent mode, thereby improving interhemispheric inhibition and hand dexterity, based on our previous findings on healthy older adults (Section 3). By doing so, this paper provides a theoretical and systematic framework for the interventions that utilize the higher plasticity of motor-cortical interhemispheric interaction and that follow its developmental rule.

2 Induction of muscle activity utilizing bilaterally active mode

To move a paralyzed hand, it is first necessary to allow muscle activity in the paretic hand to emerge. Here, we consider an intervention that maximizes the bilaterally active mode, possibly the first step in the restoration of motor function after stroke. In the case of a hemiplegic patient who cannot move the right hand but can move the left hand, we propose a method in which his/her right hand is moved passively synchronized with voluntary movement of the left hand (Figure 1A).

Recently, an intervention to restore hand motor function in hemiplegic patients by electrically contracting the muscles of the paralyzed hand in accordance with the movement of the intact hand [= contralaterally controlled functional electrical stimulation (CCFES)] has been shown to be effective (16–22). One may assume that the essence in this intervention is proprioceptive intervention of a hand synchronized with voluntary movement of the other hand (bilateral proprioceptive-motor coupling). Cunningham et al. (16) have suggested in chronic stroke patients that the CCFES may induce disinhibition of motor-cortical interhemispheric inhibition. However, changes in motor-cortical activity by a bilateral proprioceptive-motor coupling intervention remain unclear. Therefore, we first show in healthy volunteers that passive movement of one hand synchronized with voluntary movement of the other hand can effectively induce muscle activity in the former, and its related activity change in the bilateral motor cortices.

When a healthy person voluntarily moves the left hand, the right motor cortex is activated, and the left motor cortex is deactivated (inhibited) due to interhemispheric inhibition. Similarly, when the

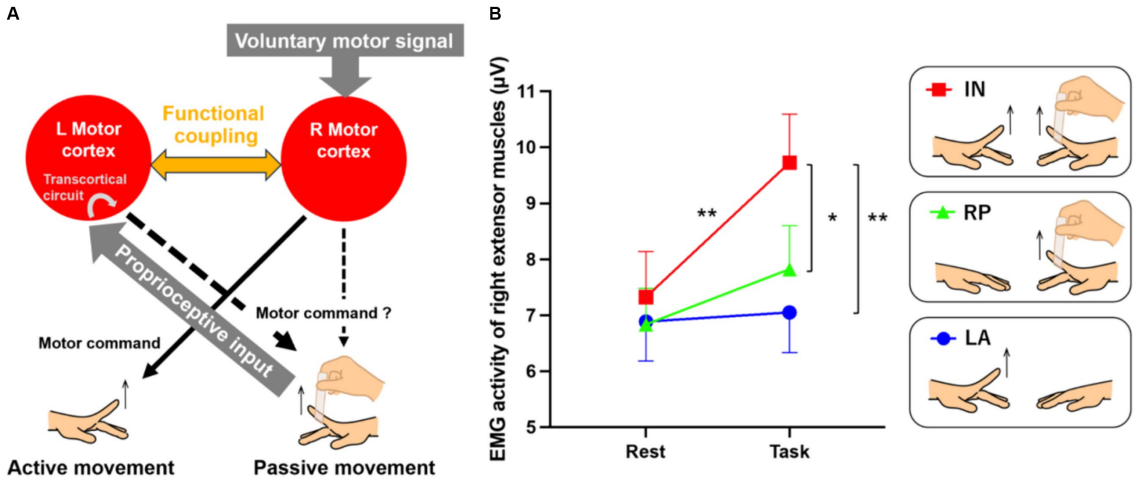

FIGURE 1
Possible neural mechanisms underlying passive extension of the right index finger synchronized with the voluntary extension of the left finger **(A)** and EMG results **(B)**. **(A)** We hypothesize that passive movement of the right hand synchronized with voluntary movement of the left hand will lead the left and right motor cortices to a bilaterally active mode, and interhemispheric functional connectivity must be enhanced between the two motor cortices. This enhanced functional coupling may allow the bilateral motor cortices to share the voluntary motor signal input to the right motor cortex and the proprioceptive input to the left motor cortex, promoting sensory-motor associations between them. If the sensory-motor association occurs in the left motor cortex, the voluntary motor signal may effectively activate the intrinsic transcortical circuit between the left motor cortex and the right hand muscles, leading to muscle activity increase in the right passively-moved finger. If this association also occurs in the right motor cortex, the cortex might also become part of the network increasing the muscle activity, in concert with the left one. **(B)** EMG results from the left active (LA; blue), right passive (RP; green), and in-phase (IN; red) tasks. Small bars on the graph indicate standard errors of the mean across participants. *$p < 0.005$, **$p < 0.001$.

right hand is moved passively, a proprioceptive signal activates the left motor cortex via somatosensory area 3a and the cerebellar vermis (23), leading to inhibition of the right motor cortex through interhemispheric inhibition (24).

We hypothesize that simultaneous voluntary movement of the left hand and passive movement of the right hand will lead the left and right motor cortices to a bilaterally active mode (Figure 1A). In this situation, interhemispheric functional connectivity must be enhanced between the motor cortices. This enhanced functional coupling may allow the bilateral motor cortices to share the voluntary motor signal input to the right motor cortex and the proprioceptive input to the left motor cortex, promoting sensory-motor associations between them. If the sensory-motor association occurs in the left motor cortex, the voluntary motor signal may effectively activate the intrinsic transcortical circuit between the left motor cortex and the right hand muscles, for instance (25, 26), increasing muscle activity during passive movement. If this association also occurs in the right motor cortex, the cortex might become part of the network increasing muscle activity, in concert with the left one.

2.1 Methods and results

We tested these hypotheses in healthy adults. The details of methods are described in Supplementary material. We recruited 55 healthy right-handed young adults (37 male, 18 female; age 19–26 years old). Their handedness was assessed by the Edinburgh Handedness Inventory (27). The motor tasks consisted of (1) a left finger active extension task (left active; LA) in which the blindfolded participants extended their left index finger to a 1 Hz tone, (2) a right finger passive extension task (right passive; RP) in which the experimenter extended the right relaxed index finger to a 1 Hz tone, and (3) an in-phase task (in-phase; IN) in which the experimenter extended the right relaxed finger (RP) synchronized with the participant's active left finger extension (LA; Figure 1B). The study protocol was approved by the Ethics Committee of the National Institute of Information and Communications Technology, and the MRI Safety Committee of the Center for Information and Neural Networks (CiNet; no. 2003260010). We explained the details of the present study to all participants before the experiment, and they then provided written informed consent. The study was conducted according to the principles and guidelines of the Declaration of Helsinki (1975).

We first examined if muscle activity in the right relaxed finger increases during the IN task. In all tasks, surface electromyograms (EMGs) were recorded from the finger extensor muscles of the right hand. The 20-s task was repeated eight times with a 10-s rest phase in between. The root-mean-square EMG values from the first 2–19 s during the task and from the first 2–7 s during the rest phase were calculated, and average values for the eight tasks and rest phases were calculated for each individual. A total of 44 of all participants showed EMG increase during the task phase compared to the rest phase in the IN task. A two-factorial analysis of variance (repeated measurement) for tasks (3) × period (2: task-rest) revealed a significant interaction [$F(2,108) = 9.21$; $p < 0.001$]. A *post hoc* test revealed a significant increase in muscle activity during the IN task compared to the rest phase ($p < 0.001$ Bonferroni corrected); further, activity during the IN task was significantly higher than during the LA and RP tasks ($p < 0.001$, $p < 0.005$ Bonferroni corrected, respectively). In other words, the IN task could effectively increase muscle activity in the right relaxed finger, an effect that could not be induced by passive movements alone (Figure 1B).

To investigate the neural substrates underlying the IN task, brain activity was measured with a 3 Tesla functional MRI during the above three tasks. Using an image analysis software of statistical parametric mapping, we preprocessed individual images, spatially smoothed them with a 4 mm Gaussian filter, and conducted statistical analyses (see Supplementary material). We adopted a voxel-wise threshold of $p < 0.005$, and evaluated the significance of brain activations in terms of the spatial extent of the activations in the entire brain or in small volume correction [SVC; $p < 0.05$, family-wise-error (FWE) corrected].

When comparing the IN task with the LA and RP tasks, bilateral motor-cortical activations were observed (Figure 2A, red). The peaks of these activations were located in M1 (cytoarchitectonic areas 4a/4p; MNI coordinates x, y, z = −38, −16, 50 and 36, −16, 52). Specifically, in the LA task, the right M1 was activated and the left M1 was deactivated while, in the RP task, the opposite was observed (Figure 2B). Hence, when performing the LA or RP task alone, there is deactivation by interhemispheric inhibition, however the IN task, which combines the LA and RP tasks, bilaterally activates motor cortices (Figures 2A,B). Since these activations were observed only during the IN task, these can be considered IN task-related motor-cortical activations, and are likely associated with sensory-motor association.

Next, using a generalized psychophysiological interaction analysis (28), we further examined the brain regions where activity enhanced functional coupling with the activity in the left or right motor-cortical cluster (Figure 2A, red) during the IN task when compared to the other tasks (see Supplementary material). The right (2,202 voxels; peak coordinates = 34, −18, 50, area 4p) or left (746 voxels; peak coordinates = −38, −20, 52, area 4p) motor-cortical activity increased their functional coupling with the left or right cluster, respectively (Figure 2A, orange).

Finally, we examined if the IN task-related motor-cortical activity (IN > LA + RP) correlates with the EMG increase (task > rest) in the right extensor muscles during the IN task across the 44 participants (see Supplementary material). In the left motor cortex, we found a significant cluster of 28 voxels (peak coordinates = −34, −14, 48; Figure 2C, left pink section), which became significant after SVC ($p = 0.021$ FWE-corrected) within a sphere with 8 mm radius around the peak of the IN task-related left M1 activity. Plotting this relationship across participants showed that the IN task-related left M1 activity was greater in participants with higher EMG activity during the IN task (r = 0.47; Figure 2D, left). Similarly, in the right motor cortex, we also found a significant cluster of 27 voxels (peak coordinates = 40, −14, 52; Figure 2C, right pink section), which became significant after SVC ($p = 0.023$ FWE-corrected) within a sphere with 8 mm radius around the peak of the IN task-related right M1 activity. The IN task-related right M1 activity was also greater in participants with higher EMG activity during the IN task (r = 0.35;

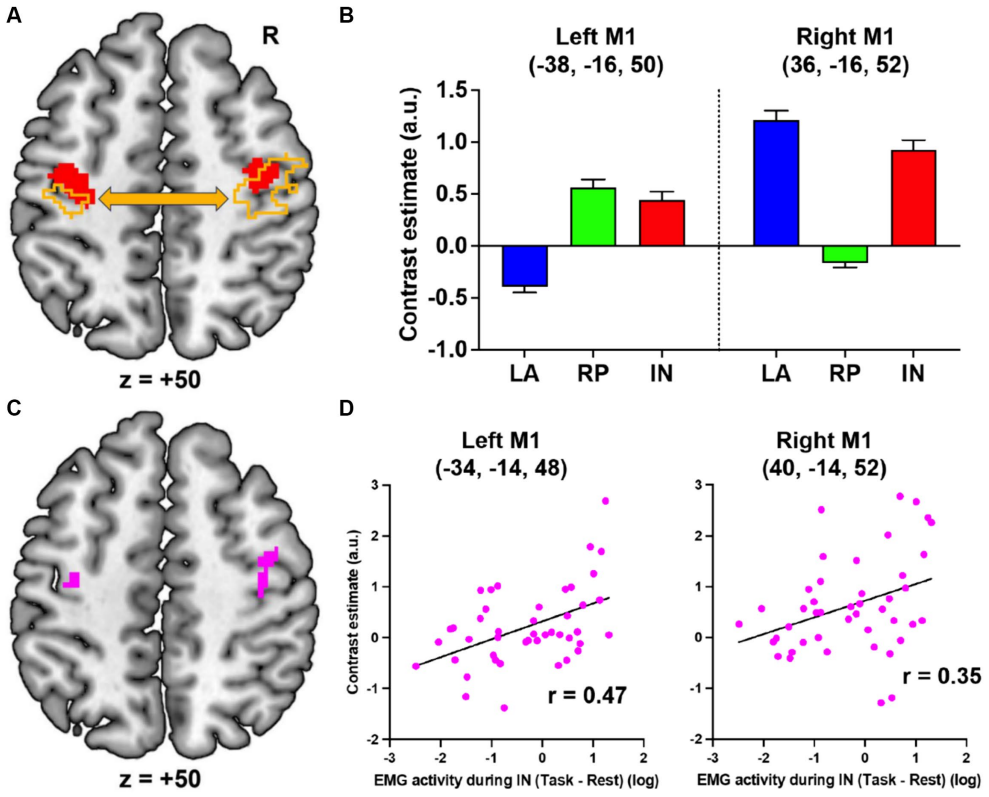

FIGURE 2
fMRI results. **(A)** Bilateral motor-cortical activations (red) when comparing the IN task with the LA and RP tasks. The left and right motor cortices (orange) in which activity enhanced functional coupling with the right or left motor-cortical cluster (red), respectively. **(B)** Brain activity in the peaks of the left and right motor-cortical clusters in each task. **(C)** The left and right motor cortices (pink) in which activity significantly correlated with the EMG activity during the IN task. **(D)** Interparticipant correlation between the left or right M1 activity and log value of EMG activity. LA, left active; RP, right passive; IN, in-phase; M1, primary motor cortex; R, right; a.u., arbitrary unit.

Figure 2D, right). The results indicate that the IN task-related bilateral motor-cortical activities are related to the EMG increase during the IN task.

2.2 Discussion and possible clinical application

The present study has clearly demonstrated in healthy volunteers that passive movement of a relaxed hand synchronized with voluntary movement of the other hand can effectively induce muscle activity in the former. This intervention leads the motor cortices to bilaterally active mode, and enhances their interhemispheric functional coupling. Further research is needed to determine how the putative sensory-motor association leads to the EMG increase. However, in the current work, not only the left (contralateral) but the right (ipsilateral) motor-cortical activity correlated with the EMG increase of the right relaxed hand (Figures 2C,D). The current work could not prove the causal relationship between these activities and the EMG increase through descending pathways. In primates, neurons in the ipsilateral motor cortex project to spinal interneurons (29, 30). Therefore, not only the contralateral but the ipsilateral activity might be directly involved in the EMG increase through the ipsilateral descending pathway. If so, the IN task could promote activity in this pathway [c.f. (31)], which could compensate hand motor function after contralateral stroke (32).

The current results were obtained from healthy young participants; therefore, the current intervention needs to be tested in stroke patients. There are several caveats to be considered when applying our intervention clinically. First, the patients must have intact proprioceptive pathways from the paralyzed side, since proprioceptive input (processing) from the paretic hand (most likely synchronized with the movement of the intact hand) could be crucial. However, even when proprioceptive pathways are damaged, viewing the movement of one's own paretic hand synchronized with the voluntary movement of the intact hand might cause similar effects to bilateral mirror therapy (33–35). Second, complete damage to the motor cortex severely impairs both motor and proprioceptive processing (36). This study showed that a right-handed 71-year-old male patient with a focal subcortical hemorrhage over the left precentral hand region was unable to move his right arm/hand/fingers and could not experience proprioceptive illusory movement of the right hand in the third week after the stroke. (These functions were improved 6 months after stroke.) On the other hand, in the case of partial motor-cortical damage by an experimental ischemic block, the motor and proprioceptive functions seems to be compensated by spared adjacent tissue around stroke core (3). Hence, in the latter case, capability of residual tissue associating motor and proprioceptive signals would be the key.

We expect that the IN task may be effective in the acute and subacute phases of stroke when the brain spontaneously shifts to the bilaterally active mode (2). We assume that moving the immobile hand from the acute and subacute phases of stroke may decrease the risk of excessive interhemispheric inhibition from the contralesional (intact) motor cortex to the ipsilesional one, as shown in chronic phase (16). In addition, such early phase intervention might decrease the risk of spasticity or rigidity progression caused by long-term immobility of the paretic hand.

In the present paper, we focused on the IN task-related activity in the bilateral motor cortices. The reality, however, is that much broader sensory-motor cortical–subcortical networks are involved (Supplementary Figure 1). In addition to the bilateral motor cortices, the IN task-related activity (IN > LA + RP) was identified in the left secondary somatosensory cortex (SII), in the right area 2, intraparietal sulcus area (IPS), inferior parietal lobule (IPL), SII, ventral premotor cortex (PMv)/area 44, and in the left cerebellar hemisphere and vermis. The right inferior parieto-frontal cortices and the left cerebellar hemisphere and vermis are main constituents of proprioceptive processing network (23, 37). Hence, sensory-motor association during the IN task likely occurs not only in the bilateral motor cortices but also in the proprioceptive processing network. This means that a bilateral proprioceptive-motor coupling intervention allows for intervention not only in the bilateral motor cortices as previously thought, but also in the broader proprioceptive network. If one considers the fact that the PMv is capable of sending motor commands to the spinal cord (30) and of compensating motor function when the M1 is severely damaged (38, 39), proprioceptive-motor coupling in this region could be advantageous for recovery of hand motor function. Finally, one should bear in mind the possibility that the right inferior parieto-frontal and the left cerebellar damages may reduce the effectiveness of this intervention (40).

3 Improvement of hand dexterity utilizing left–right independent mode

The bilaterally active mode is accompanied by involuntary muscle activity and movement. After stroke, when the motor cortex ipsilateral to the hand is active, involuntary mirror movements and muscle activity of the opposite hand can occur (4, 41). Involuntary mirror movements and muscle activity can also be observed in children with immature interhemispheric inhibition between the left and right motor cortices and in older adults with reduced interhemispheric inhibition (42). Such involuntary movements are more likely to appear when the bilaterally active mode is overtrained. In addition, excessive activity in the motor cortex ipsilateral to the hand in children and older adults is closely related to their lower hand dexterity (24, 43). To circumvent this, training the motor cortex into a left–right independent mode, by training the left and right hands to perform different movements, may be effective. Indeed, the previous study has shown in healthy older adults that their left and right motor cortices become bilaterally active mode, probably due to aging-related decline of interhemispheric inhibition, but that 2-month bimanually different movement training can reactivate the inhibition and improve hand dexterity (24).

The bilaterally active mode of the left and right motor cortices observed in healthy older adults is similar to that observed after stroke. When the bilateral motor-cortical activation is a cause for the clumsiness of movement when a stroke patient becomes able to manage to move the paretic hand, training both hands to perform different movements could improve his/her interhemispheric inhibition and hand dexterity.

4 Conclusion

Our recent EMG and functional MRI study in healthy younger adults suggests that proprioceptive intervention of the paralyzed

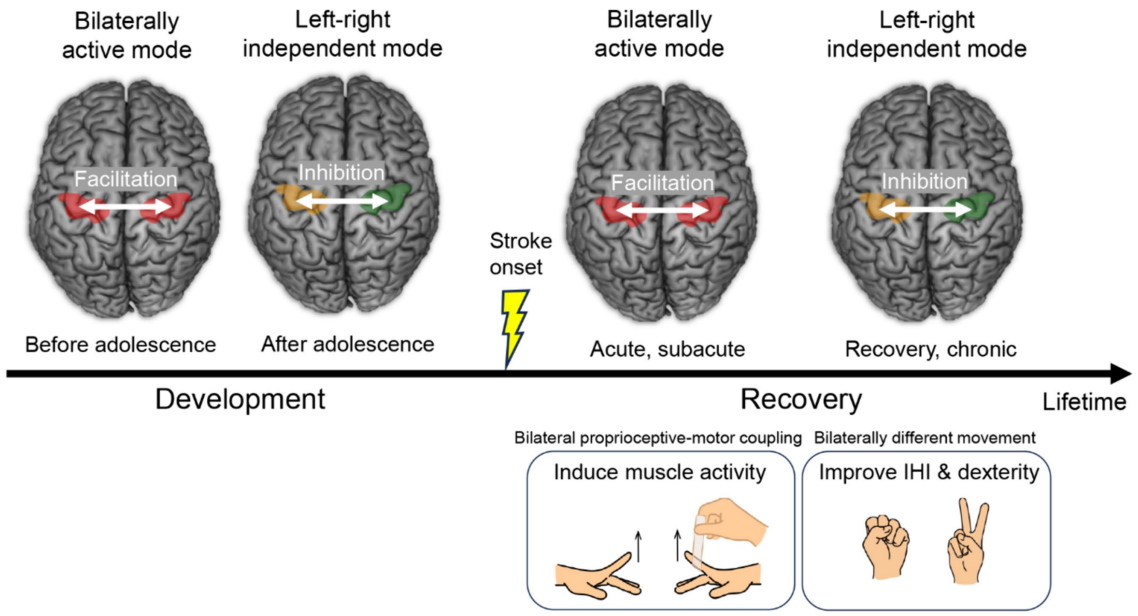

FIGURE 3
Transition of the left and right motor cortices from the bilaterally active mode to the left–right independent mode. This is a rule of typical development of hand motor function and also a common feature of motor function recovery after stroke. Proposed interventions during recovery are shown at right bottom. IHI, interhemispheric inhibition.

(immobile) hand synchronized with voluntary movement of the intact hand (bilateral proprioceptive-motor coupling intervention) could be worth applying for restoration of motor function of the paretic hand after stroke, utilizing the spontaneous bilaterally active mode of motor cortices frequently observed after stroke (Figure 3). This way, muscle activity could be induced in the paralyzed hand through the association between voluntary motor signals and proprioceptive inputs to the motor cortex. In addition, our previous functional MRI study in healthy older adults indicates the possibility that, when a stroke patient becomes able to manage to move the paretic hand but the movement is clumsy, training both hands to perform different movements (bilaterally different movement training) that guides the motor cortices into left–right independent mode could improve interhemispheric inhibition and hand dexterity (Figure 3). These are not a one-size-fits-all theory that can solve problems of all stroke patients (44). However, one could expect that the series of proposed interventions give a beneficial effect on hand motor functions of certain types of stroke patients.

The transition of the motor cortices from the bilaterally active mode to the left–right independent mode is a common feature of motor function recovery after stroke (2, 4), and also is a rule of development of hand motor function (Figure 3), which everyone has experienced during the developmental process (9, 10). The habilitation of "re-habilitation" means "to gain ability," and it is during the developmental period that the most ability is gained in a person's lifetime. Therefore, rehabilitation according to developmental rules may be the most natural and effective way for the brain to reacquire abilities. When planning rehabilitation strategies, taking advantage of the brain's spontaneous recovery process and referring to its developmental rules may be important considerations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Minoru Tsukada, Ethics Committee of the National Institute of Information and Communications Technology. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HN: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EN: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1408324/full#supplementary-material

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Efficacy and safety of deep brain stimulation in mesencephalic locomotor region for motor function in patients with post-stroke hemiplegia: a study protocol for a multi-center double-blind crossover randomized controlled trial

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Background: Deep brain stimulation (DBS) is a potential treatment for improving movement disorder. However, few large-sample studies can reveal its efficacy and safety. This study aims to initially explore the efficacy and safety of DBS in the mesencephalic locomotor region (MLR) on motor function in patients with post-stroke hemiplegia.

Methods/design: This multicenter, prospective, double-blind, randomized crossover clinical trial aims to assess the safety and effectiveness of Deep Brain Stimulation (DBS) in the mesencephalic locomotor region (MLR) for patients with moderate to severe post-stroke hemiplegia. Sixty-two patients with stable disease after a year of conservative treatment will be enrolled and implanted with deep brain electrodes. Post-surgery, patients will be randomly assigned to either the DBS group or the control group, with 31 patients in each. The DBS group will receive electrical stimulation 1 month later, while the control group will undergo sham stimulation. Stimulation will be discontinued after 3 and 6 months, followed by a 2-week washout period. Subsequently, the control group will receive electrical stimulation, while the DBS group will undergo sham stimulation. Both groups will resume electrical stimulation at the 9th and 12th-month follow-ups. Post-12-month follow-up, motor-related scores will be collected for analysis, with the Fugl-Meyer Assessment Upper Extremity Scale (FMA-UE) as the primary metric. Secondary outcomes include balance function, neuropsychiatric behavior, fall risk, daily living activities, and quality of life. This study aims to provide insights into the therapeutic benefits of DBS for post-stroke hemiplegia patients.

Result/conclusion: We proposed this study for the first time to comprehensively explore the effectiveness and safety of DBS in improving motor function for post-stroke hemiplegia, and provide evidence for DBS in the treatment of post-

stroke hemiplegia. Study limitations are related to the small sample size and short study period.

Clinical Trial Registration: Clinicaltrials.gov, identifier NCT05968248.

KEYWORDS

deep brain stimulation, hemiplegia, motor dysfunction, motor recovery, stroke

Introduction

The number of stroke patients worldwide has exceeded 20 million, making it the third largest disease burden in the world after cardiovascular disease and cancer, causing economic losses to society and patients' families (1, 2). The disability rate of stroke is as high as 60%–80% (2), among which post-stroke hemiplegia is the main reason for the high disease burden (3). Currently, there is no particularly effective clinical treatment. Post-stroke hemiplegia may result in permanent disability if they do not receive timely and effective treatment (3, 4). The high cost of traditional rehabilitation, coupled with the cumbersome rehabilitation training methods, family commuting, poor treatment effects, and other factors make it difficult for patients to adhere to treatment or the treatment effects are few (5). In recent years, innovative rehabilitation strategies to improve motor function, represented by deep brain stimulation, have emerged (6–9). Deep brain stimulation can provide long-term chronic stimulation, and adjust the stimulation parameters during follow-up (10–12). Fine-tuning the treatment has achieved better therapeutic effects in many diseases that were difficult to treat in the past, such as Parkinson's disease and depression (13, 14). Therefore, it has been used to improve motor function recovery after stroke and has been confirmed by human clinical studies. In a phase I clinical trial conducted by Baker et al. in 2023, 12 patients with moderate to severe upper limb motor deficits after unilateral stroke received cerebellar dentate nucleus-DBS treatment (7, 15). After treatment, the patient's upper limb Fugl-Meyuer motor function scores improved by 7 points, the motor function of the upper limbs was significantly improved, and no serious complications occurred during the treatment (7).

The mesencephalic locomotor region (MLR) is critical for motor recovery (16–19). The MLR (Figure 1) is a phylogenetically conserved key motor control center in the brainstem, which is composed of two leading nuclei, namely the Pedunculopontine Nucleus (PPN) and the cuneate nucleus (CNF) (20–23). PPN is associated with exploratory behavior, and deep brain stimulation (DBS) of PPN in patients with Parkinson's disease can reverse the freezing of gait (16, 23–28). CNF is the main control area for movement initiation, maintenance, and speed regulation, and research on stimulating this target with DBS to improve incomplete spinal cord injury (SCI) has aroused scientific and clinical interest (29, 30). Electrical stimulation of the rat MLR in an acute rodent stroke model to achieve near-physiological hindlimb movements during walking and swimming (20), and MLR-DBS improved walking speed and limb coordination (31). The MLR-DBS study confirmed that MLR-HFS does not affect the infarct area, however, it can regulate the area around the lesion and reduce neuroinflammation by affecting the cholinergic anti-inflammatory pathway (32–35). In particular, CNF high-frequency stimulation (HFS) can significantly reduce the neuroinflammation at the stimulation site. Inflammatory cytokines and chemokines, reduce the concentration of pro-inflammatory cells (23, 33). In addition, DBS can stimulate CnF glutamatergic neurons, activate their afferent or efferent fibers, and stimulate spinal reticular fibers to initiate movement within a short latency period (32, 33, 36–39). Judging from the above literature, MLR-DBS is a potentially effective treatment for post-stroke motor dysfunction, but the application of DBS in the treatment of post-stroke sequelae is still in the exploratory stage, and a large number of studies are still in the animal experiment and clinical verification stages (40). No large-sample clinical trials have been conducted. So we designed this multi-center randomized controlled clinical trial (RCT) (7). The leading purpose is to explore the safety and effectiveness of DBS in improving motor function in patients with post-stroke hemiplegia. The secondary purpose is to explore its potential therapeutic mechanism and provide clinical evidence support for the widespread application of DBS technology in post-stroke hemiplegia.

Methods and analysis

Study design

The trial is a multicenter, prospective, double-blind crossover randomized controlled trial (RCT). The overall process is in Figure 2. In this study, we will include 62 moderate to severe post-stroke hemiplegia patients who had stable disease after 1 year of conservative treatment in multiple neuro medical centers in the General Hospital of the People's Liberation Army of China et al. All patients included in the study will undergo deep brain electrode implantation. They will be randomly postoperatively divided into a DBS group and a control group, with 31 patients in each group. 1 month after surgery, the DBS group will be given electrical stimulation treatment, while the control group will undergo routine observation. Following up in the 3rd and 6th months after surgery. After the follow-up, all patients will stop electrical stimulation treatment for 2 weeks. After the 2-week washout period, the control group will start electrical stimulation treatment, and the DBS group will continue observation. Outpatient follow-up in the 6th and 9th months after surgery. After the follow-up, all patients will undergo electrical stimulation treatment. Observe for a long time. The leading outcome measure of follow-up is the pre-and post-change score on the Fugl-Meyer Assessment Upper Extremity Scale (FMA-UE). In addition, we will follow up on changes in the secondary outcomes of balance function, neuropsychiatric behavior, Post-stroke Spasticity, fall risk, activities of daily living, and quality of life.

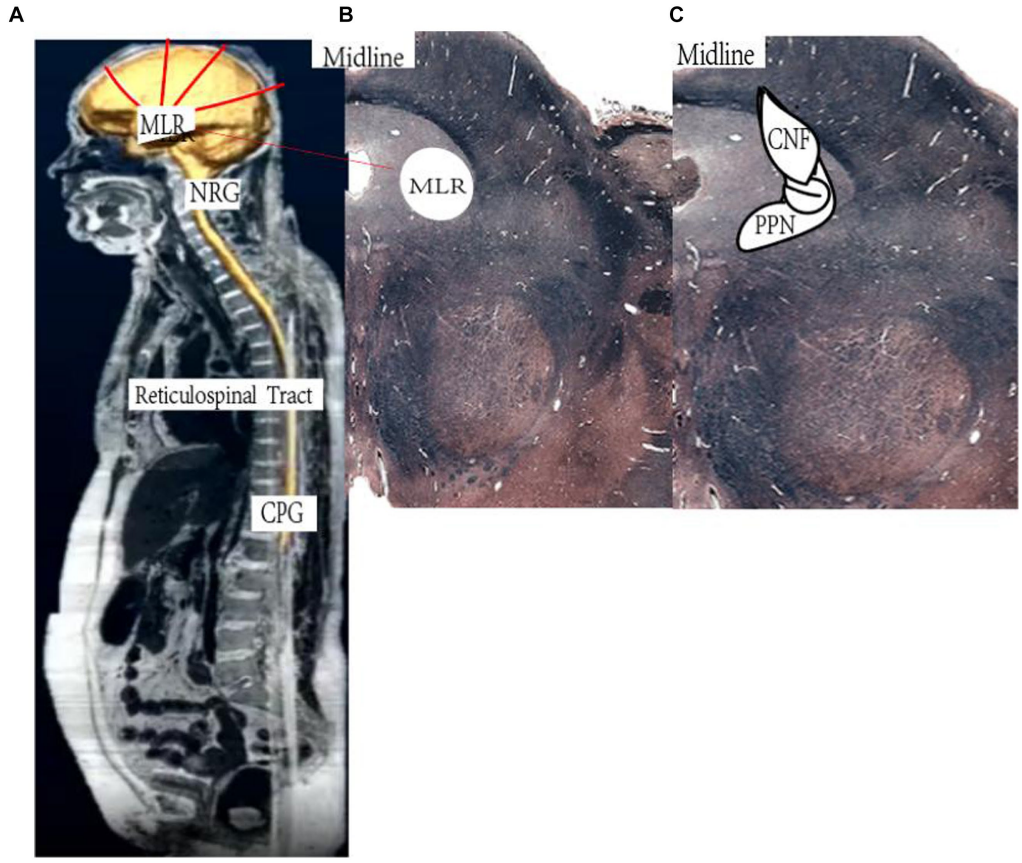

FIGURE 1
Schematic illustration of the reticulospinal system. **(A)** Higher central nervous system centers of motion control send their signals to the mesencephalic locomotor region (MLR). The MLR is bilaterally linked to its downstream target, the gigantocellular reticular nucleus (NRG), which gives rise to the reticulospinal tract and drives the central pattern generators (CPG) for motoneuron activation and locomotion. **(B,C)** Horizontal section of the human **(B)** and cross section of the rat **(C)** midbrain at the level of the superior colliculi depicting the MLR (**B**: landmarks based on Afshar et al. 90; **C**: landmarks based on Paxinos and Watson 91). CNF, cuneiform nucleus; PPN, pedunculopontine nucleus. Based on https://www.neuroanatomy.ca/index.html.

Methods

Sample size

This study is a randomized, double-blind, active sham stimulation control design, and statistical experts determined that the sample ratio between the DBS group and the control group was 1:1. A review of the literature revealed that subjects' upper limb FMA scores improved by an average of 7 points. Since this study was based on the changes in the mean FMA before and after DBS treatment, based on literature data, the mean FMA before DBS treatment was 21.92 ± 6.30, and the mean FMA after DBS treatment was 35.42 ± 12.23. This study is designed as a difference test to determine whether the mean of the DBS group (u1) is different from the mean of the control group (u2) (41, 42). The assumptions are as follows: H0: $u1 - u2 = 0$, H1: $u1 - u2 \neq 0$. The two-sided significance level was 5%, the statistical power was 90%, and the dropout rate was 20% (43). The total sample size required for this study was calculated by PASS V.15 sample size calculation software to be 48 patients, with 24 people in each group. According to the possibility of electrode implantation deviation and other special circumstances leading to a lose, we included 62 patients, 31 in each group.

Enrollment

Researchers will publish recruitment information through the hospital website, designate dedicated personnel to consult patients and their families via telephone and video connections, conduct preliminary screening based on the exclusion criteria (Table 1), and recommend qualified patients to bring complete relevant examinations, test data, and cases to the hospital. In the outpatient clinic, qualified neurosurgery clinicians will further evaluate and diagnose the patients. Eligible patients will be enrolled, and the researcher will give full informed consent and sign an informed consent form. The evaluators will collect surgical baseline data based on the case report form (CRF). The patient will be admitted to the hospital 1 week before the operation. After admission, general preoperative examinations and tests will be completed, including an electrocardiogram, chest X-ray, hematuria and stool routine, coagulation screening, blood type identification, biochemistry, and eight preoperative items. Then, the patient will be evaluated by professional evaluators. The main evaluation contents will include an assessment of motor function, mental behavior, quality of life, past disease history, and related treatment drugs and measures.

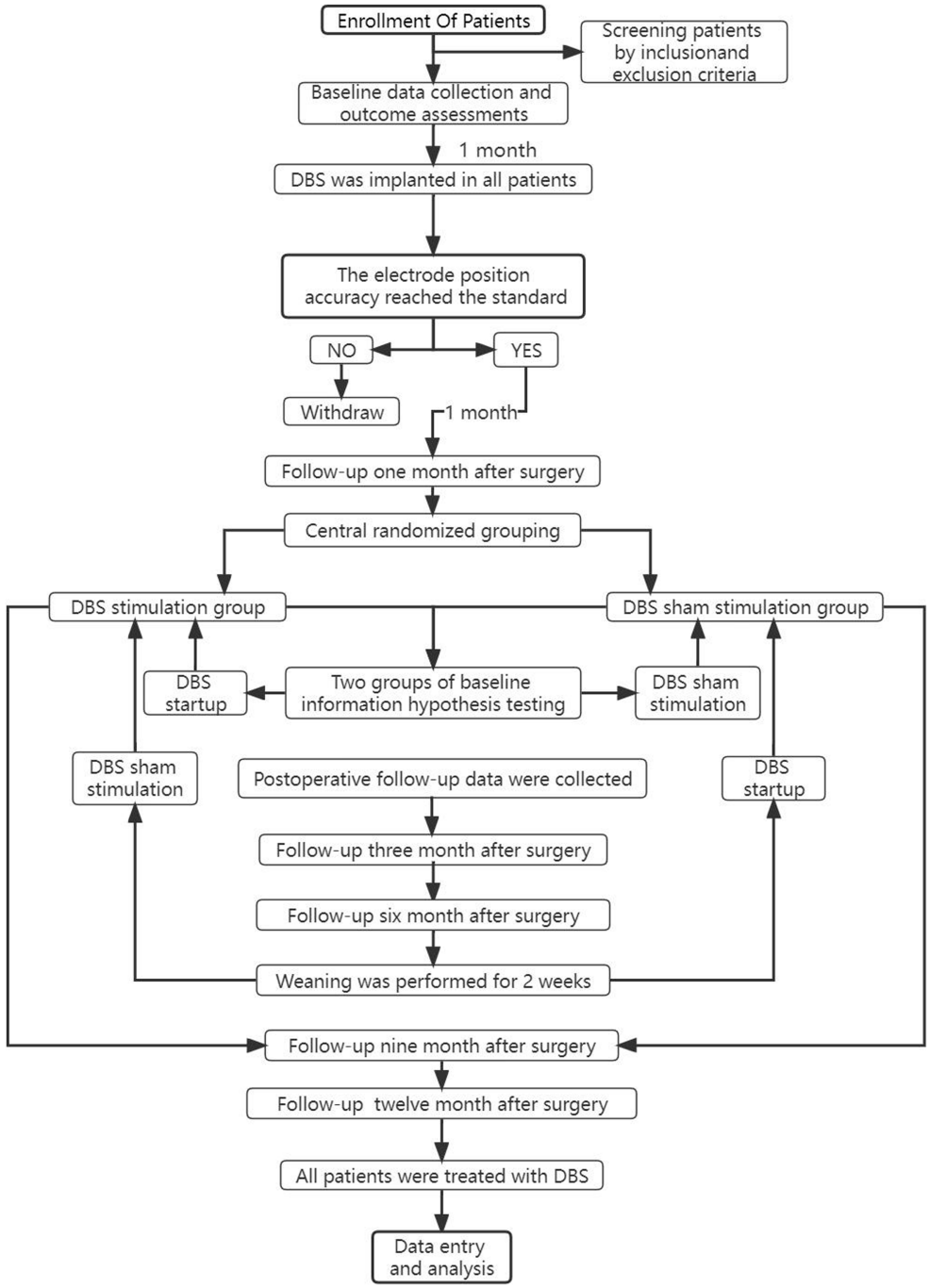

FIGURE 2
Brief flowchart of the entire study with draw. For patients whose electrode is not implanted in the ideal position in CT review after DBS implantation, the device can be temporarily left off, and the follow-up of clinical trials is excluded, and relevant conventional rehabilitation means can be actively given. The health status of patients can be observed at any time, and regular follow-up can be conducted. When all clinical trials are over, the effect of DBS treatment can be observed. If the effect of DBS treatment is better than that of the traditional control group, the electrode position should be adjusted again and DBS treatment should be performed again.

Finally, the day before the operation, the examiner will arrange for the patient to undergo a brain MRI examination. The examination results will be burned into a CD and handed over to a dedicated person for safekeeping. On the day of the operation, the surgical planning system (ELEKTA) will be introduced for preoperative planning, including electrode implantation paths and treatments (44).

Interventions

The process of MLR-DBS for post-stroke hemiplegia is in Figure 3. All individuals in the study will receive bilateral stereotactic implantation of intracranial leads under general anesthesia. The patient will be installed with a Leksecl-G directional device under general anesthesia in the operating room and undergo MRI positioning scanning in the MRI room during the operation. Default

TABLE 1 List of inclusion and exclusion criteria.

Inclusion	Exclusion
(1) Meet WHO or International diagnostic criteria for post-stroke hemiplegia;	(1) Glasgow Coma Scale (GSC) score below 15, Minimum Mental State Examination (MMSE) assessment for dementia indicated, suffering from mental disturbance and unable to cooperate with examination or treatment.
(2) The first unilateral supratentorial ischemic stroke, the condition is stable after acute treatment of ischemic stroke, the course of disease is ≥1 year, and participate in 2 evaluations (screening and baseline) before enrollment.	(2) Motor and sensory disturbances are not induced by stroke, nor by previous ischemic stroke, but stroke induced by trauma, brain tumor, etc.
(3) Diagnosed by professional physicians combined with brain CT or magnetic resonance imaging and other imaging techniques;	(3) Serious comorbidities, such as malignant tumors, primary heart, liver, kidney or hematopoietic system diseases.
(4) Between the ages of 18 and 80, male or female	(4) History of cognitive impairment, mental disorder, drug abuse, drug allergy, and alcoholism.
(5) The responsible lesion in the unilateral white matter area indicated by cranial CT or MRI	(5) Previous craniotomy, thrombectomy and thrombolysis.
(6) Relevant sequelae such as limb dysfunction after stroke, accompanied by unilateral limb motor dysfunction, proved to be right-handed by standardized examination.	(6) Possess a pacemaker, metal stent, plate, or implant susceptible to electrical impulses in the body (pacemaker or defibrillator, baclofen pump, deep brain stimulator, Ventricular shunts, shrapnel, etc.).
(7) There is obvious motor disorder, FMA motor function score is between 50 and 84;	(7) Pregnant or breast-feeding or have a recent birth plan.
(8) Perfect clinical data	(8) Clinical data are perfect.
(9) Stable medical and physical condition with adequate nursing support and appropriate medical care in the patient's home community.	(9) Congenital or acquired abnormalities of lower extremities (affecting joints and bones).
(10) The patient himself or voluntarily signs the informed consent and is willing to cooperate with relevant treatment.	(10) Registration of investigators, their family members, employees, and other dependents.
Withdrawal criteria	(11) Severe joint contractures cause loss or limitation of lower limb activities.
(1) After the start of the clinical study, it is found that the subjects do not meet the case inclusion criteria;	(12) Blood system diseases with increased risk of bleeding during surgical intervention.
(2) There is no data after enrollment;	(13) Participate in another study drug study within 30 days before and during this study.
(3) Subjects have poor compliance and have never used the experimental treatment plan;	(14) Unable to complete the basic process, or difficult to maintain compliance and follow-up.
(4) Those who seriously violate the experimental protocol.	
Termination criteria	
Continuation of the study may harm the relevant rights and interests of a certain number of subjects	

CnF coordinates will be calculated from the MRI brainstem landmarks to target the brainstem normalized coordinates and use the diffusion tract map to ensure we target the medial, superior cerebellar, and central peduncles, within the area demarcated by the lid (Figure 4). Before DBS lead placement, microelectrode recording and test stimulation will be performed to assess intraoperative physiology and rule out potential side effects that may require repositioning of the lead. First, electrophysiological mapping of CNF will be performed. Microelectrodes will be precisely inserted along predefined trajectories, directed toward the CNF, and connect the neuromodulation system and manual actuators to the stereotaxic device. The center of this area shows neuronal responses to imaginary walking, which stimulates passive and active lower body movements while the patient performs a series of motor tasks with their lower body suspended from the operating table. As this study is the first to investigate DBS of CNF in patients with post-stroke movement disorders, there are no guidelines for optimal stimulation parameters. However, comparable evidence accumulated from preclinical studies in various animal models suggests that low-frequency stimulation (≤50 Hz) at moderately wide pulse widths (200–1,000 μs) may be possible due to the evolutionary conservation of the MLR in mammalian species properties (45). Therefore, we first stimulated with increasing voltage at 20 Hz, 400 μs, 2.0–4.5 V pulse width, and then adjusted the frequency and pulse width based on individual intraoperative behavioral responses. Intraoperative MRI and postoperative CT will be used to determine whether the electrode insertion position will be deviated and whether the operation will be completed after checking for accuracy.

Randomization

The 62 patients will be enrolled in the group undergoing deep brain electrode implantation. The 62 patients will be randomly divided into two groups at a ratio of 1:1 using a simple random grouping method, with 31 patients in the DBS group and the control group.

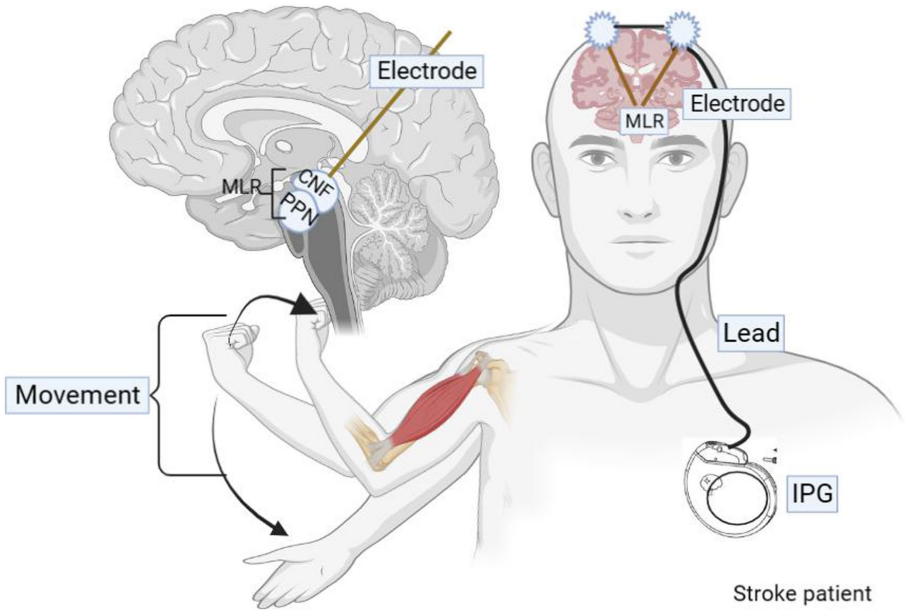

FIGURE 3
Graphic of DBS delivery during therapy sessions. During the in-clinic rehabilitation session, for each movement effort, the clinician/therapist generates the DBS pulse via a push button connected to a laptop computer. A Wireless Transmitter, attached to the laptop, triggers the patient's implanted pulse generator to deliver the DBS pulse.

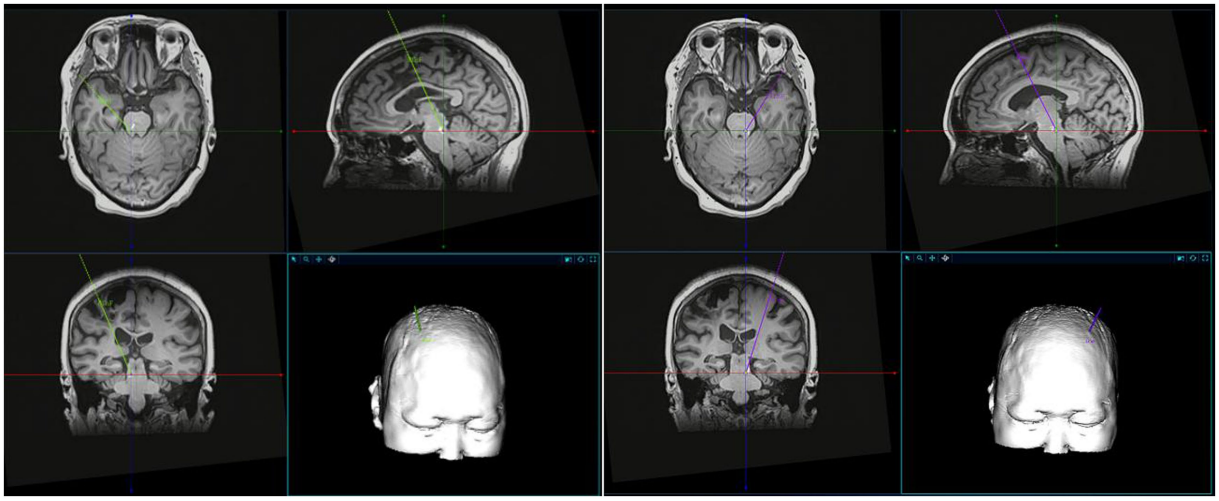

FIGURE 4
A schematic representation of the MLR localization. MLR localization was performed in combination with preoperative imaging, stereotactic map of human brain and related literature.

First, random numbers will be automatically generated by the OpenClinica clinical trial data management platform to achieve centralized randomization. When a new patient meets the inclusion and exclusion criteria and signs the informed consent form, each research center can apply for the patient's randomization number after filling in the patient's basic information in OpenClinica. The random numbers will be automatically issued by the system, and only one coordinator in each center has access. All patients included in the study will receive DBS implantation after baseline assessment and were then randomly divided into two groups in a 1:1 ratio: DBS treatment group and control group. The former will start electrical stimulation treatment 1 month after the operation. Specialists will assess the patient's recovery status through the remote rehabilitation system every week and guide rehabilitation training and electrical stimulation treatment. The latter will receive the same rehabilitation training under the face-to-face guidance of experts, except for the power-on (sham stimulation, the power-on stimulation parameter was 0). Experts will evaluate the patient's recovery and adjust rehabilitation strategies every week in the outpatient clinic. The study is blinded to participants, scale raters, and data analysts. Allocation information will be kept in opaque, sealed envelopes by a designated person not involved in the study, thus ensuring the concealment of random assignment.

TABLE 2 Participant timeline of data collection.

Study period	Screening	Perioperative period		Follow-up period				
	Enrollment	Allocation/ surgery	Postsurgery	1 month	3 month	6 month	9 month	12 month
Number of days	15 ± 7	10 ± 7	3 ± 2	7 ± 3	7 ± 3	7 ± 3	7 ± 3	7 ± 3
Enrollment								
Eligibility screen	×							
Informed consent	×							
Medical history	×							
MRI scanning	×		×					
Interventions								
MLR-DBS surgery		×						
Stimulation parameters		×						
Allocation								
DBS group				×	×	×		
Control group							×	×
Assessments								
Primary outcome measure								
FMA	×		×	×	×	×	×	×
Secondary outcome measures								
BBS	×		×	×	×	×	×	×
POMA	×		×	×	×	×	×	×
BI	×		×	×	×	×	×	×
SF-36	×		×	×	×	×	×	×
HAMD	×		×	×	×	×	×	×
AE		×	×	×	×	×	×	×

Blind method

To ensure study quality, all operators, therapists, patients, evaluators, and analysts will remain blinded to assignments and interventions until data collection, analysis, and video recording are completed. During video recording, patients wear surgical caps to conceal the data collection time point. These videos will be uploaded to a central unit and scored by two neurologists, without knowledge of whether the patient is receiving DBS treatment. The data administrator will label the groups as A and B for analysis. However, to safeguard patient safety, the operating doctor cannot be blinded to provide timely treatment in case of emergency. Overall, patient safety is our utmost priority (44).

Outcome measurements

All outcome measures will be evaluated by professional research assistants 1 week before surgery, during the perioperative period, and at one-month, three-month, six-month, nine-month, and 12-month intervals postoperatively (Table 2). All measurement results will be securely uploaded to a third-party online data management system. The primary outcome measure is the improvement in patients' motor function before and after deep brain stimulation, assessed primarily through changes in the Fugl-Meyer Assessment Upper Extremity Scale (FMA-UE). Secondary indicators include the evaluation of patients' balance function, neuropsychiatric behavior, fall risk, activities of daily living (ADL), and quality of life before, after, and at various time points following treatment, along with the calculation of the stroke improvement rate.

Main outcome

Motor function intervention effect

The main evaluation index of this study is the improvement of patients' motor function before and after deep brain stimulation, which is being evaluated through changes in the Fugl-Meyer Assessment Upper Extremity Scale (FMA-UE) (7). FMA-UE is widely

used in clinical motor function assessment and is a quantitative stroke-specific scale used to assess motor function, balance, sensation, and joint function in patients with hemiplegia. Each of the five areas contains different assessment items that are scored on a 3-point scale. This scale has good validity and reliability in the stroke population. The scale covers 50 items, with a total score of 226 points (46). There are 17 sports items, with a total score of 100 points, of which the upper limb motor function score is 66 points, the lower limb motor function score is 34 points. The higher the assessment score, the better the patient's motor function (47).

Secondary outcome

Balance ability

Stroke patients suffer from balance dysfunction due to impaired control of the brain's central nervous system and sensory or motor conduction pathways. The Berg Balance Scale (BBS) is mainly used to evaluate the balance and coordination abilities of participants during intervention and follow-up (48, 49). This scale is suitable for patients with strokes of various severity. Through assessment, it can identify whether patients need help with their movements and prompt the patient's prognosis. It is mainly used in subacute and chronic strokes to predict and evaluate balance after stroke. It has reliability and validity, sensitivity is good, and it is currently the most commonly used international balance scale for stroke patients. The form includes a total of 14 items, each item includes 5 levels (0 to 4 points), with a total score of 56 points. Higher scores indicate better balance ability (49, 50).

Post-stroke Spasticity will be evaluated using the modified Ashworth Scale (MAS), a widely-used assessment method. It measures resistance during passive joint movements, especially suitable for patients with hemiplegia. Muscle spasticity is graded from 0 to 4, with higher grades indicating increased tone. MAS has proven reliable and valuable in clinical settings for assessing upper limb muscle spasticity. Notably, up to 97% of chronic stroke patients with moderate to severe motor impairments experience spasticity (51–53).

Fall risk

Falls after stroke are common sequelae of poor motor function recovery, which can cause fear of walking, lead to prolonged hospitalization, increase the risk of disability and death, and seriously affect the independence and quality of life after stroke. Performance-oriented activity assessment (POMA) will be used to assess fall risk during intervention and follow-up. A previous study reported that the POMA is an easy-to-administer task-oriented test with higher test weight than other tests such as the time remaining test, one-leg stance test, and functional accessibility test. Reliability, discriminant validity, and predictive validity (54, 55). The total possible score is 28, the lower the score, the greater the risk of falling (56).

Activities of daily living

About 75% of stroke patients suffer from varying degrees of disability, and in severe cases, they even lose the ability to take care of themselves (57). In the process of stroke rehabilitation, the training of self-care ability in daily life is also very important and necessary. Participants' ability to perform activities of daily living will be assessed by the Barthel Index (BI) during the intervention and follow-up periods (58, 59). BI is a widely used clinical assessment method for daily living ability. It can be used not only to evaluate functional status before and after treatment, but also to predict treatment effects, length of stay, and prognosis. It has the advantages of simple evaluation, strong operability, high reliability, and high sensitivity. Previous studies have shown that BI has high internal and external reliability in assessing the daily living activities of stroke survivors. BI consists of 10 items describing different activities, with a total score of 100 points. The higher the score, the better the patient's independence and the lower the dependence on others.

Quality of life

Patients with improved motor function are often accompanied by improved quality of life. Effective rehabilitation treatment can improve the quality of life after stroke, help patients restore function, improve self-confidence and self-esteem, and reintegrate into social life. This study mainly used a 36-item short-form questionnaire (SF-36) to assess patients' quality of life. The scale includes 8 aspects and 36 items (60–62). It is easy to use, accepted by patients and meets strict reliability and validity standards. A higher assessment score represents a higher quality of life for the patient.

Psychological improvement

Patients with post-stroke hemiplegia may develop post-stroke depression (PSD), which is characterized by persistent depressed mood disorder (mood disorder). The overall incidence rate is as high as 40% to 50%, of which about 15% are severe depression, which may be accompanied by severe suicide or even suicidal behavior. This study used the Hamilton Depression Rating Scale (HAMD) for evaluation (63). This scale is simple to operate, has high reliability and validity, and is widely used in clinical applications. Among them, the HAMD-24 is the most clinically used. Therefore, this study evaluated patients before and after HAMD-24 treatment. A total score of more than 8 points indicates the presence of depressive symptoms in patients, and the higher the score, the more severe the depressive symptoms.

Adverse events

During the treatment process, a small number of patients may experience symptoms such as accidental injuries, skin rupture and bleeding, muscle soreness, joint pain, and rashes. Any adverse events (AEs) during recovery should be documented in a specific CRF with time of occurrence, severity, relationship to the duration of the intervention, and prognosis. Investigators should take necessary measures to deal with all AEs to ensure the safety of the subjects and follow up with the subjects until their physical condition returns to normal levels. All adverse events (such as pain and falls) occurring during intervention and follow-up will be recorded on a case record form (CRF) through monitoring and self-reporting, and the relevance of the intervention will be assessed. The incidence of an adverse event was defined as the number of patients in whom it occurred divided by the number of all patients. Calculate the number and frequency of adverse events, related adverse events (adverse reactions), adverse events leading to withdrawal, and serious adverse events, and provide detailed records (64, 65).

Data management and analysis

Data management

Before the study begins, all researchers receive comprehensive training on the protocol so that subjects have a clear understanding of the testing requirements subjects can better cooperate and provide more realistic information during the testing process. During the follow-up period, oral medications can be needed, but medications that may significantly interfere with the study results are prohibited from being used as auxiliary treatment. All medications should stopped 24 h before each follow-up assessment. If discomfort during the period, a remote program control should be carried out in time to adjust the stimulation parameters. The follow-up method is mainly outpatient follow-up. When irresistible factors occur, telephone contact and WeChat video connection can be temporarily used instead. However, during subsequent outpatient visits, all information obtained from the last non-outpatient visit must be shared with the patient. Check with your family members to ensure the authenticity and accuracy of the information. All researchers will use unified, standardized, normative, and internationally accepted assessment scales and case report forms (CRF). Before surgery, perioperatively, and 1 month, 3 months, 6 months, 9 months, and 12 months after surgery, blinded professional evaluators strictly followed the standardized evaluation scale and evaluation process to conduct evaluations and record standardized videos. Professional clinicians not related to this study will re-evaluate the scores at each follow-up time point and compare the scores obtained with the first score. If the difference is not significant, the first evaluation results will used. If the difference is too big, a third evaluation will performed. Once the assessment results are accurate, the recorder uploads the data to the case report form. During the data collection process, two data supervisors will review the contents of CRF to ensure the authenticity and accuracy of the data. If there are data errors or incomplete information, the data manager sends it back to the appropriate center, where the researcher checks the original file, rechecks, and updates the data. At the end of the trial, the data administrator will lock the database and send the data separately to two data analysts for analysis. During the research process, to ensure the quality and accuracy of the data, only designated personnel not related to this study can view and modify the data, and each modification will be recorded, and personnel related to this trial will remain evasive throughout the process.

Data analysis

All data analysis will based on IBM SPSS Statistics 25.0, describing the total score of each scale at each follow-up and the change from baseline at each visit after treatment. Measurement data using mean ± standard deviation to describe. Count data Use numerical values (%) to describe, and use group t-test or Wilcoxon to compare between groups according to the characteristics of the data. Intra-group comparisons were performed using rank sum-test, paired t-test or paired signed rank-test. For comparisons of pre-and post-treatment change values based on baseline general information, appropriate multivariate analysis models were used to correct for the effects of confounding factors or covariates based on the data situation. The single-item count data of each scale used the chi-square test or the exact probability test, and the grade data used the Wilcoxon rank sum test. A paired rank sum test and repeated measures analysis of variance were used to analyze the changes in score data within the group before and after treatment. The effectiveness measurement index is the improvement rate of each clinical scale at different follow-up times = (scale score at each postoperative time point − preoperative score) / preoperative score * 100%. A score improvement rate > 25% is considered effective. Safety observation indicators are all postoperative adverse reactions, including surgery-related adverse reactions, device-related adverse reactions, and stimulation-related adverse reactions. The type, number of cases, occurrence time, treatment measures, and prognosis of adverse events are recorded. The incidence of adverse events is defined as the number of patients in which it occurs divided by the number of all patients, and an adverse event rate of less than 5% is considered safe.

Data monitoring

The entire implementation of this study will be regularly supervised and guided by specialized personnel assigned by the Ethics Committee of the People's Liberation Army General Hospital who have no interest in this study. All information related to adverse (AEs), protocol revisions, and protocol deviations will be reported to the Ethics Committee. During enrollment and follow-up evaluation, a third-party data management company assigns dedicated personnel to supervise to ensure the accuracy and objectivity of the evaluation. After the evaluation, a third-party data management company assigned a dedicated person to conduct data verification. After verification, two blind research assistants entered all the collected data into the online data management system through double-entry. Before conducting descriptive and statistical analyses, data checks (CRF checks, and duplicate checks on raw data) were performed to ensure data accuracy. Access to the data set is restricted to clinical trial management and the data safety and monitoring board. The storage and processing of research data will strictly comply with the regulations and policies of the researcher's institution and research site. In addition, serious adverse events will be reported in detail to the Ethics Committee of the PLA General Hospital and the independent Data Safety and Monitoring Committee, which will recommend whether to continue, modify, or stop the intervention. During the research process, data sets will be stored, analyzed, and archived pseudonymously to protect personal privacy.

Research difficulties

A particular challenge remains trajectory planning and lead implantation. Compared with the rodent PPN and CNF, many regions of the human brainstem, including MLR subnuclei, are small and poorly described. Based on known coordinates in PPN DBS, the frozen gait symptom in Parkinson's disease patients can be successfully reduced to landmarks in human and rodent stereotaxic atlases to map the relationship of CNF to PPN. To improve the accuracy of planning trajectories and intraoperative positioning, a more detailed description of the macroscopic and microscopic anatomy of human MLR is urgently needed.

Discussion

The study is currently being conducted at multiple centers including the Chinese People's Liberation Army General Hospital. At present, research on the application of DBS in post-stroke motor dysfunction is gradually carried out (66). Slotty et al. (67) used GPi-DBS combined with Vim/ventral nucleus (Vop)-DBS to treat a case of unilateralism secondary to putamen stroke. In studies on patients with dystonia, the results showed that the patient's motor symptoms were significantly and sustainably improved; Elias et al. included nine studies with a total of 32 patients with post-stroke dyskinesia and found that at least 13 of the patients received DBS treatment (12). Post-motor symptoms improved significantly. Koerbel et al. (68) reported a 48-year-old patient after a thalamic hemorrhagic stroke. After DBS zona incerta (ZI) treatment, the patient's proximal motor function was significantly improved, the abnormal involuntary movement scale score was significantly reduced. Franzini et al. (15) reported that the motor function of 3 patients with post-stroke motor function deficits improved after DBS treatment of the contralateral internal capsule posterior limb. Baker et al. (7) used cerebellar dentate nucleus-DBS to treat 12 patients with moderate to severe upper limb motor deficits after unilateral stroke. The patients' upper limb Fugl-Meyuer motor function score increased by 7 points, and the upper limb motor function improved. There was no improvement during the treatment. Serious complications occur. For patients with post-stroke motor dysfunction, the range of stimulation parameters is wide and needs to be adjusted individually according to the stimulation target. Existing literature shows that the optimal stimulation parameters must be determined individually for each patient. The optimal stimulation parameters have not yet been established. The conclusion is still under intense discussion. Paro et al. (12) systematically analyzed 82 DBS electrodes implanted in 53 patients and found that the voltage [M (range)] of 55 leads was 3.4 (2.4~4.0) V, the frequency [M (range)] of 63 leads is 145 (130~185) Hz, and the pulse width [M (range)] is 90 (60~120) μs. However, there are also studies showing that wider pulses (>400 μs) appear to be more effective in enhancing movement and more convenient than shorter pulse widths, and preliminary results from local field potential (LFP) measurements and behavioral tests suggest that lower stimulation frequencies (8–20 Hz) are more appropriate, therefore, we first stimulated with 20 Hz, 400 μs, 2.0–4.5 V pulse width, increasing voltage, and then adjusted the frequency and pulse width according to individual intraoperative behavioral responses. Although a large number of relevant studies have been carried out to initially confirm the unique advantages, effectiveness, and safety of DBS in patients with post-stroke hemiplegia, they are still at the stage of basic animal experiments, case reports and case series reports and large-sample RCTs have not yet been carried out. Research to confirm its effectiveness and safety. Based on this, we designed this research protocol. To our knowledge, this trial protocol is the first to explore the effect of MLR-DBS on improving motor function in stroke survivors. It is also the first RCT in the field of application of DBS in post-stroke motor dysfunction. Research proposal. This multicenter, prospective, randomized, double-blind crossover controlled clinical research protocol is the first to develop and execute a study on the safety, feasibility, and safety of deep brain stimulation (DBS) in the midbrain motor region (MLR) to improve motor dysfunction after stroke plan. The evaluation results were evaluated by random shuffling, and the first evaluation was blindly evaluated with standardized videos for comparison before and after to reduce potential bias. The randomization process of this study was carried out after the surgery of all patients, thus avoiding to a large extent the interference on the study results caused by the surgeon's inability to implement blinding. Our research team has performed thousands of deep brain electrode implantation surgeries to treat Parkinson's disease, dystonia, Major syndrome, and other diseases, and has rich clinical and surgical experience. The main purpose of this trial protocol is to improve wheelchair, subacute, and chronic stroke motor dysfunction through MLR-DBS and to study the clinical feasibility and efficacy of MLR-DBS in humans. Study results will demonstrate the effectiveness, efficacy, and safety of MLR-DBS in improving motor function in stroke survivors. Our goal is to maximize the long-term restoration of lost motor function in patients with severe movement disorders. This research program will guide on the importance of integrating existing and different rehabilitation techniques and designing more effective rehabilitation programs. The results of this trial will help to understand the neural mechanisms of MLR-DBS in stroke patients who develop hemiparesis after stroke. Provide clinical evidence support for the large-scale clinical application of DBS technology.

At the same time, this research protocol also has some shortcomings and the following areas that need improvement. First, the sample size is small and limited to the chronic phase of stroke patients, so the results cannot be generalized to the wider stroke population. Spontaneous recovery and potential complications of stroke heterogeneity are more evident in patients with acute and subacute ischemic stroke, and further studies in a larger number of patients may be warranted. Secondly, the sham operation group in our study did not receive electrical stimulation. For the sake of patient interests and ethical requirements, the sham stimulation group will not last for a long time and cannot completely imitate real-world research. This configuration is a sham. The weakest version of the control group, since electrical stimulation is likely to be detected in the active DBS group, while in the sham group, there is no electrical stimulation. Third, open-loop DBS was applied in our study, but closed-loop neuromodulation is more effective than open-loop neuromodulation, and closed-loop DBS should be investigated in future studies. Fourth, the ideal stimulation parameters of DBS are one of the most critical challenges for its application, as these parameters have a huge impact on clinical efficacy. The optimal timing of DBS initiation and many optimal parameters such as stimulation site and side, electrode and waveform configuration, efferent or afferent stimulation, and titration regimen are unknown. Our treatment parameters may affect treatment outcomes. In the future, larger-scale clinical trials and clinical practice applications are needed to confirm the actual application effect of DBS. It is necessary to discuss treatment parameters in future studies.

Advantages and limitations

Advantages

This multicenter, prospective, randomized, double-blind crossover clinical study is the first to investigate the feasibility and

safety of midbrain motor region (MLR) deep brain stimulation (DBS) in improving motor dysfunction after stroke. To minimize bias, we will use standardized videos for blinded evaluation and randomly disrupt the evaluation results before and after the initial assessment. The randomization process will occur post-surgery, ensuring surgeons' blinding and preventing study interference. Our team has extensive experience in deep brain electrode implantation surgeries for Parkinson's disease, dystonia, and other conditions. Additionally, we will conduct significant basic research on MLR-DBS, achieving promising results currently being compiled for publication.

Limitations

While this surgery-related study has taken measures to minimize the surgeon's impact on blinding, patient safety remains paramount. In cases of adverse reactions, urgent unblinding may be necessary, potentially affecting experimental accuracy.

Dissemination

The findings will be published in a peer-reviewed journal, and the publication will be published on an "open access" clause, making the dataset accessible to research investigators and statistical evaluators. Research results will also be distributed to participants, stakeholders and policy makers (Beijing Municipal Commission of Economy and Informatization, Beijing Municipal Commission of Health and Family Planning). Researchers will be responsible for publishing the study, sharing the results with the wider scientific community, regardless of the size or direction of the effect.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Chinese PLA General Hospital. All research procedures complied with the current version of the Declaration of Helsinki (see www.wma.net for details) and relevant ethical guidelines. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. The research team will communicate study information, including study objectives, recruitment criteria, study protocol, potential risks, and expected functional benefits to recruiting participants. Participants will be informed that they may withdraw from the study at any time without consequences.

Author contributions

JX: Investigation, Writing – original draft. BL: Investigation, Writing – review & editing. SL: Supervision, Writing – review & editing. ZF: Methodology, Software, Writing – review & editing. YZ: Formal analysis, Validation, Writing – review & editing. DL: Writing – review & editing. QC: Writing – review & editing. HY: Formal analysis, Writing – review & editing. YC: Conceptualization, Writing – review & editing. XY: Resources, Visualization, Writing – review & editing. ZM: Funding acquisition, Resources, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Innovative prognostication: a novel nomogram for post-interventional aneurysmal subarachnoid hemorrhage patients

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Background and purpose: Spontaneous aneurysmal subarachnoid hemorrhage (aSAH) is a common acute cerebrovascular disease characterized by severe illness, high mortality, and potential cognitive and motor impairments. We carried out a retrospective study at Fujian Provincial Hospital to establish and validate a model for forecasting functional outcomes at 6 months in aSAH patients who underwent interventional embolization.

Methods: 386 aSAH patients who underwent interventional embolization between May 2012 and April 2022 were included in the study. We established a logistic regression model based on independent risk factors associated with 6-month adverse outcomes (modified Rankin Scale Score ≥ 3, mRS). We evaluated the model's performance based on its discrimination, calibration, clinical applicability, and generalization ability. Finally, the study-derived prediction model was also compared with other aSAH prognostic scales and the model's itself constituent variables to assess their respective predictive efficacy.

Results: The predictors considered in our study were age, the World Federation of Neurosurgical Societies (WFNS) grade of IV-V, mFisher score of 3–4, secondary cerebral infarction, and first leukocyte counts on admission. Our model demonstrated excellent discrimination in both the modeling and validation cohorts, with an area under the curve of 0.914 ($p < 0.001$, 95%CI = 0.873–0.956) and 0.947 ($p < 0.001$, 95%CI = 0.907–0.987), respectively. Additionally, the model also exhibited good calibration (Hosmer-Lemeshow goodness-of-fit test: $X^2 = 9.176$, $p = 0.328$). The clinical decision curve analysis and clinical impact curve showed favorable clinical applicability. In comparison to other prediction models and variables, our model displayed superior predictive performance.

Conclusion: The new prediction nomogram has the capability to forecast the unfavorable outcomes at 6 months after intervention in patients with aSAH.

KEYWORDS

aneurysmal subarachnoid hemorrhage, interventional embolization, prediction model, functional outcomes, validation

Introduction

Spontaneous Aneurysmal Subarachnoid Hemorrhage (aSAH) is a common and acute cerebrovascular condition that is often seen in neurological emergency departments. It is characterized by its profound severity and is connected with high mortality rates and enduring disability. As a result, it can place substantial socio-economic burdens on both society and afflicted families.

Several scoring systems or prediction models have been established to evaluate prognosis after aSAH, including the aSAH prognostic prediction model developed from the Subarachnoid Hemorrhage International Trialists (SAHIT) (1) multinational cohort study, the Functional Recovery Expected after Subarachnoid Hemorrhage (FRESH) (2), and the SAFIRE grading scale developed by van Donkelaar et al. (3). It is worth noting that these scoring systems are typically designed to apply to a broad spectrum of subarachnoid hemorrhage cases. Currently, surgical interventions are crucial in the management of aSAH patients. Microsurgical aneurysm clipping and endovascular interventional embolization not only prevent rebleeding, but also potentially mitigate severe complications such as cerebral herniation, hydrocephalus, and vasospasm. It is noteworthy that different treatments may exert varying influences on patient prognosis. Therefore, the refinement and stratification of study populations enable the attainment of more precise predictive results.

Nevertheless, most existing studies on prediction models in aSAH patients demonstrate notable deficiencies in terms of comprehensive and practical predictive methods. For instance, they frequently fall short in the collection of relevant biomarkers from both blood and cerebrospinal fluid during prognostic investigations, thereby neglecting the potentially pivotal role of neurobiology in anticipating outcomes after aSAH (4, 5). Furthermore, some prediction models primarily gather data related to preoperative patient conditions while disregarding critical elements such as intraoperative rebleeding, acute thrombosis formation, delayed cerebral ischemia, and others (6). Additionally, certain studies have focused on populations with unique living environments, lifestyle habits, and genetic backgrounds, limiting the predictive value of their models for the broader Chinese population (7). To establish accurate and reliable prediction models, further exploration is needed.

To overcome these limitations, we sought to develop a model to predict the 6-month prognosis of patients with aSAH undergoing endovascular aneurysm embolization, with the goal of helping clinicians to identify high-risk and to provide a more proactive treatment strategy.

Materials and methods

Patient selection

Our study collected data at an early stage on all patients with spontaneous aSAH who underwent interventional embolization at our hospital and branch hospitals between May 2012 and April 2022. The cases collected at our hospital constituted the modeling cohort, while those collected at our branch hospital were used as validation cohort.

Inclusion criteria: (1) age > 18 years and the first occurrence of aSAH; (2) onset of symptoms within 72 h and confirmed the etiology of SAH as intracranial aneurysm rupture through head Computed Tomography (CT) and/or whole-brain Digital Subtraction Angiography (DSA) examinations; and (3) underwent endovascular embolization treatment.

Exclusion criteria: (1) non-aneurysmal causes of subarachnoid hemorrhage; (2) coexistence of other cerebrovascular diseases such as arteriovenous malformation, arteriovenous fistula, moyamoya disease; (3) patients with severe systemic diseases before the onset of the condition, such as hematological disorders, immune system disorders, recent history of central nervous system infection or other infectious diseases, severe cardiopulmonary, hepatic, and renal insufficiencies; (4) pregnant and postpartum women; and (5) patients with incomplete or lost follow-up data during hospitalization.

The Fujian Provincial Hospital Ethics Committee authorized this retrospective observational study (K2021-07-044).

Data collection

We collected the patients' basic status information during hospital admission, which included demographic and clinical characteristics (8, 9), time of onset, laboratory examination and medical histories, such as diabetes and hypertension. The study scope also covered clinical assessments and In-hospital care, including clinical scores that evaluate aSAH severity (10–14), characteristics of the aneurysm (4), timing of interventional surgery, cerebrospinal fluid drainage (15), post-rupture complications, duration of mechanical ventilation, and length of hospital stay (16). Post-rupture complications included secondary cerebral infarction (17, 18), rebleeding (19, 20), pulmonary infection (21, 22), hydrocephalus, seizures (23, 24), cerebral herniation and cardiac events (25). In particular, secondary cerebral infarction refers to new cerebral ischemic lesions occurring after spontaneous subarachnoid hemorrhage due to various possible reasons such as vasospasm, thrombus formation, delayed cerebral ischemia, etc.

Prognostic outcome measures

Clinical follow-up of patients was conducted at 6 months postoperatively through outpatient visits and telephone consultations. The prognosis was evaluated using the modified Rankin Scale (mRS), where a score of 0–2 indicated a positive prognosis and a score of 3–6 indicated an unfavorable prognosis.

Statistical analysis

The statistical analyses were executed using the software SPSS 25.0 and R 4.2.2. Quantitative data that conformed to normal distribution were expressed as mean ± standard deviation (SD), while non-normally distributed quantitative data were presented as median and interquartile range (IQR). Counts and percentages [cases (%)] were used for categorical data. Student's *t*-test or Mann–Whitney U test was employed for the comparison of quantitative variables, as appropriate, and the chi-square test or Fisher's exact test was utilized for comparing categorical variables. Multicollinearity was assessed using the tolerance and variance inflation factor (VIF). To identify independent risk factors associated with unfavorable outcomes at

6 months, only variables from the univariate analysis that had a significance level of $p \leq 0.01$ were included in the multivariate logistic regression analysis using a backward stepwise regression. The associations were conveyed by using odds ratios (ORs) along with their respective 95% confidence intervals (CIs).

The prediction model was crafted utilizing the rms package in the R language. The evaluation of the prediction model's performance involved the utilization of the following validation methods. The plotting and calculation of ROC curves and AUC for both the modeling and validation cohorts were conducted using the pROC package. The rms package was used to plot and calculate the calibration curves and brier scores for the two cohorts, while the ResourceSelection package was utilized to conduct the Hosmer-Lemeshow test. The rmda package was employed for generating clinical decision curves and clinical impact curves for both cohorts, and the caret package was used to run the bootstrap self-sampling method. Finally, the riskRegression package and pROC package were utilized to compare the ROC curves of the prediction model with those of other aSAH prognostic rating scales and the component variables of the model.

Results

Patient characteristics

Our study collected data at an early stage on all patients with spontaneous aSAH who underwent interventional embolization at our hospital and branch hospitals between May 2012 and April 2022, a total of 446 cases. Of these, 60 patients were excluded, including one patient under 18 years old, five readmitted due to recurrent episodes, two cases where embolization was terminated during surgery, eight cases where no aneurysm was found on angiography, 19 cases with symptom onset beyond 72 h, and 25 cases lost to follow-up. Thus, the final 386 cases were included in the study. Of the 258 patients who underwent interventional embolization at our hospital from May 2012 to April 2022, they were included as the modeling cohort. The number of such patients at our branch hospital from April 2017 to April 2022 was 128, and they were included as the validation cohort. Both independent sets were further categorized into groups denoting either favorable or unfavorable outcomes based on the functional recovery at 6 months after onset.

Variable selection

Tables 1–3 show the modeling cohort's univariate analysis results. Adverse prognosis in aSAH patients with interventional embolization is related with age ($p < 0.001$), respiratory rate ($p < 0.001$), GCS (Glasgow Coma Scale) score ($p < 0.001$), WFNS (World Federation of Neurological Surgeons) grade ($p < 0.001$), mFisher grade ($p < 0.001$), Hunt-Hess grade ($p < 0.001$), first leukocyte counts on admission ($p < 0.001$), neutrophil count ($p < 0.001$), lymphocyte count ($p = 0.002$), monocyte count ($p = 0.003$), D-dimer level ($p < 0.001$), duration of mechanical ventilation ($p < 0.001$), number of cerebrospinal fluid drainage modalities ($p < 0.001$), secondary brain infarction ($p < 0.001$), pulmonary infection ($p < 0.001$), hydrocephalus ($p = 0.001$), brain herniation ($p < 0.001$), and cardiac events ($p < 0.001$).

Multicollinearity tests revealed high multicollinearity between GCS (Tol 0.040, VIF 24.824) and WFNS (Tol 0.062, VIF 16.195), as well as between the first white blood cell count (Tol 0.029, VIF 34.450) and the first neutrophil count on admission (Tol 0.032, VIF 30.845). To address this multicollinearity issue, GCS and the first neutrophil count on admission were excluded. Instead, WFNS and the first leukocyte counts on admission, along with other clinically significant variables identified through univariate analyses, were included in the multivariable logistic regression analysis. The multivariable backward stepwise logistic regression analysis showed that age ($p < 0.001$, OR = 1.085, 95%CI = 1.044–1.128), WFNS grade of IV-V ($p = 0.018$, OR = 3.746, 95%CI = 1.248–11.241), mFisher grade of 3–4 ($p = 0.018$, OR = 2.903, 95%CI = 1.198–7.035), secondary brain infarction ($p < 0.001$, OR = 12.966, 95%CI = 5.218–32.222), and the first leukocyte counts on admission ($p < 0.001$, OR = 1.326, 95%CI = 1.153–1.525) were identified as independent risk factors of a 6-month adverse outcome (Table 4).

Construction of nomogram

We combined independent risk predictors of 6-month adverse outcomes into a logistic regression model and ultimately constructed a nomogram to predict the risk of unfavorable outcomes at 6 months for patients with aSAH undergoing interventional embolization (Figure 1).

Validation of nomogram

Discrimination evaluation

The nomogram's discrimination ability was assessed using the ROC curve, with an AUC of 0.914 ($p < 0.001$, 95%CI = 0.873–0.956) for the predictive model in the modeling cohort and 0.947 ($p < 0.001$, 95%CI = 0.907–0.987) for the predictive model in the validation cohort (Figure 2).

Calibration evaluation

Calibration curve plots and the Hosmer-Lemeshow goodness-of-fit test were used to assess the calibration of the nomogram. The Brier score for the modeling cohort was 0.097, and the Brier score for the validation cohort was 0.078. Additionally, both calibration curves showed a high degree of overlap with the standard curve, indicating good consistency between the clinical prediction model and the actual outcomes (Figure 3). The Hosmer-Lemeshow goodness-of-fit test was also performed, with the results showing $X^2 = 9.176$ and $p = 0.328$ (>0.05) for the modeling cohort, and $X^2 = 11.348$ and $p = 0.183$ (>0.05) for the validation cohort.

Evaluation of clinical applicability

The clinical applicability of the nomogram was assessed using clinical decision curve analysis (DCA) and clinical impact curve (CIC). From the DCA, in the modeling cohort, the nomogram used to predict the risk of adverse outcomes showed greater net benefits when the threshold probability ranged from 6 to 100% compared to all patients or none of them treated with intervention embolization. In the validation cohort, the nomogram showed greater net benefits when the threshold probability was between 2 to 88% and 95 to 100% compared to all patients or none of them treated with intervention embolization (Figure 4). From the CIC, when the threshold probability

TABLE 1 Baseline information of the aSAH study cohort.

Variables	Modeling cohort (N = 258)				Validation cohort (N = 128)	
	Favorable outcome (n = 182)	Unfavorable outcome (n = 76)	Value	p	Favorable outcome (n = 95)	Unfavorable outcome (n = 33)
Demographic characteristics						
Male, n (%)	102 (56)	44 (57.9)	0.075[b]	0.785	58 (61.1)	17 (51.5)
Age, mean ± SD, (year)	53.3 ± 10.7	61.0 ± 12.2	−4.795[a]	**<0.001**	55.7 ± 10.1	59.1 ± 12.3
Medical history						
Hypertension, n (%)	98 (53.8)	43 (56.6)	0.162[b]	0.688	51 (53.7)	16 (48.5)
Diabetes, n (%)	17 (9.3)	6 (7.9)	0.138[b]	0.710	7 (7.4)	3 (9.1)
Smoking, n (%)	44 (24.2)	13 (17.1)	1.557[b]	0.212	22 (23.2)	6 (18.2)
Drinking, n (%)	32 (17.6)	10 (13.2)	0.770[b]	0.380	10 (10.5)	3 (9.1)
Admission condition						
temperature, median[IQR], (°C)	36.6 (36.5, 36.8)	36.7 (36.5, 36.9)	−1.268[c]	0.205	36.7 (36.5, 37.0)	36.7 (36.5, 36.8)
Heart rate, median[IQR], (times/min)	77 (68, 84)	79 (71, 88)	−1.669[c]	0.095	77 (70, 85)	79 (75, 82)
Respiratory frequency, median[IQR], (times/min)	20 (19, 20)	20 (20, 21)	−3.975[c]	**<0.001**	20 (19, 20)	20 (19, 20)
MAP, mean ± SD, (mmHg)	101 ± 15	104 ± 16	−1.641[a]	0.102	108 ± 15	110 ± 24
GCS, n (%)			41.959[b]	**<0.001**		
3–8	9 (4.9)	23 (30.3)			2 (2.1)	13 (39.4)
9–12	6 (3.3)	9 (11.8)			8 (8.4)	8 (24.2)
13–15	167 (91.8)	44 (57.9)			85 (89.5)	12 (36.4)
WFNS, n (%)			41.266[b]	**<0.001**		
I-III	167 (91.8)	44 (57.9)			85 (89.5)	12 (36.4)
VI-V	15 (8.2)	32 (42.1)			10 (10.5)	21 (63.6)
mFisher, n (%)			35.176[b]	**<0.001**		
0–2	155 (85.2)	38 (50.0)			74 (77.9)	7 (21.2)
3–4	27 (14.8)	38 (50.0)			21 (22.1)	26 (78.8)
Hunt-Hess, n (%)			33.883[b]	**<0.001**		
I–III	176 (96.7)	55 (72.4)			93 (97.9)	18 (54.5)
VI–V	6 (3.3)	21 (27.6)			2 (2.1)	15 (45.5)

[a] is the t-value, [b] is the chi-square value, and [c] is the Z-value. The bold values mean the results of the univariate analysis in the modeling queue are statistically significant.

was >20%, the nomogram categorized several individuals as "positive" (high risk) in close concordance with the count of true positives, both within the modeling cohort and the validation cohort (Figure 5).

Evaluation of generalizability

The generalizability of the nomogram was assessed using the bootstrap method, to avoid underfitting or overfitting of the nomogram. The findings indicated that it demonstrated good accuracy and stability in predicting adverse outcomes (Accuracy = 0.861, Kappa = 0.646).

Comparison with other aSAH prognostic scoring systems and its relevant variables

In the modeling cohort, the nomogram derived from the study was compared with traditional and well-established aSAH prognostic scoring systems. The nomogram showed a significantly higher AUC

TABLE 2 First laboratory indicator information of the aSAH study cohort.

Variables	Modeling cohort (*N* = 258)				Validation cohort (*N* = 128)	
	Favorable outcome (*n* = 182)	Unfavorable outcome (*n* = 76)	Value	*p*	Favorable outcome (*n* = 95)	Unfavorable outcome (*n* = 33)
WBC, median[IQR], ($\times10^9$/L)	9.14 (6.93, 11.21)	11.02 (9.24, 13.70)	−5.003[c]	**<0.001**	9.90 (8.20, 11.60)	12.50 (10.50, 16.60)
NEUT, median[IQR], ($\times10^9$/L)	7.22 (5.30, 9.11)	9.67 (7.42, 12.54)	−5.803[c]	**<0.001**	8.00 (6.50, 9.58)	10.70 (9.06, 14.95)
LYM, median[IQR], ($\times10^9$/L)	1.20 (0.90, 1.57)	0.95 (0.64, 1.38)	−3.123[c]	**0.002**	1.20 (0.90, 1.60)	0.70 (0.55, 1.15)
MONO, median[IQR], ($\times10^9$/L)	0.49 (0.35, 0.65)	0.58 (0.41, 0.79)	−2.924[c]	**0.003**	0.51 (0.37, 0.65)	0.67 (0.51, 0.90)
RBC, median[IQR], ($\times10^{12}$/L)	4.06 (3.76, 4.51)	3.95 (3.64, 4.43)	−1.669[c]	0.095	4.13 (3.77, 4.41)	4.03 (3.43, 4.45)
Hb, median[IQR], (g/L)	120 (113, 133)	120 (106, 128)	−1.659[c]	0.097	127 (113, 136)	122 (105, 141)
PLT, median[IQR], ($\times10^9$/L)	199.0 (162.0, 225.7)	184.5 (159.5, 237.5)	−0.567[c]	0.570	215.0 (186.0, 250.0)	182.0 (141.0, 238.0)
ALB, median[IQR], (g/L)	43.00 (39.30, 45.00)	41.00 (38.25, 44.19)	−1.500[c]	0.134	43.00 (41.00, 46.00)	43.00 (39.00, 46.00)
Glu, median[IQR], (mmol/L)	6.83 (5.84, 8.30)	7.57 (6.18, 9.07)	−2.235[c]	0.025	6.73 (5.82, 8.42)	8.00 (7.05, 9.38)
CK, median[IQR], (U/L)	82.50 (48.10, 149.75)	98.17 (65.00, 229.25)	−2.279[c]	0.023	84.00 (56.00, 130.00)	125.00 (70.50, 243.51)
CK-MB, median[IQR], (U/L)	12.45 (9.00, 17.03)	14.00 (9.90, 19.10)	−1.757[c]	0.079	15.00 (11.00, 20.00)	19.10 (15.50, 27.50)
K+, mean ± SD, (mmol/L)	3.78 ± 0.40	3.70 ± 0.57	1.183[a]	0.239	3.77 ± 0.50	3.79 ± 0.54
Na+, mean ± SD, (mmol/L)	138.62 ± 4.09	138.98 ± 5.50	−0.515[a]	0.607	139.05 ± 3.26	139.96 ± 4.91
COP, mean ± SD, (mmol/L)	297.02 ± 9.01	298.38 ± 12.24	−0.862[a]	0.391	296.60 ± 7.26	301.98 ± 12.46
PT, median[IQR], (sec)	11.80 (10.88, 12.90)	11.40 (10.60, 12.70)	−1.679[c]	0.093	11.10 (10.60, 11.70)	11.10 (10.70, 11.95)
APTT, median[IQR], (sec)	26.90 (22.80, 33.00)	25.75 (23.25, 32.23)	−0.699[c]	0.484	24.90 (23.60, 26.90)	25.40 (23.15, 27.05)
Fib, median[IQR], (g/L)	2.88 (2.41, 3.61)	3.13 (2.66, 3.96)	−2.116[c]	0.034	2.83 (2.29, 3.39)	2.61 (2.46, 3.17)
D-dimer, median[IQR], (mg/L)	1.27 (0.71, 3.43)	2.80 (1.51, 5.49)	−4.005[c]	**<0.001**	1.14 (0.52, 2.43)	2.93 (1.77, 5.23)

[a] is the *t*-value, [b] is the chi-square value, and [c] is the Z-value. The bold values mean the results of the univariate analysis in the modeling queue are statistically significant.

of 0.914 (95%CI = 0.873–0.956) compared to the Hunt-Hess grading system with an AUC of 0.622 (95%CI = 0.569–0.674) and the WFNS grading system with an AUC of 0.669 (95%CI = 0.610–0.729). These differences were statistically significant (Table 5; Figure 6).

Furthermore, in the modeling cohort, the nomogram was compared with its component variables. The nomogram demonstrated a greater AUC of 0.914 (95%CI = 0.873–0.956) compared to age with an AUC of 0.677 (95%CI = 0.604–0.750), WFNS with an AUC of 0.669 (95%CI = 0.610–0.729), mFisher with an AUC of 0.676 (95%CI = 0.614–0.738), secondary brain infarction with an AUC of 0.708 (95%CI = 0.647–0.769), and initial leukocyte counts on admission with an AUC of 0.698 (95%CI = 0.628–0.767) (Figure 7). We further compare the created models with the previously presented SAHIT, SAFIRE, and Fresh models, the results of which we show in the Supplementary material.

TABLE 3 Data on the aSAH study cohort during hospitalization.

Variables	Modeling cohort (N = 258)				Validation cohort (N = 128)	
	Favorable outcome n = 182	Unfavorable outcome n = 76	Value	p	Favorable outcome n = 95	Unfavorable outcome n = 33
LOS, median[IQR], (days)	16 (12, 19)	17 (11, 22)	−1.353[c]	0.176	15 (11, 18)	25 (11, 38)
MV duration, median[IQR], (days)	0 (0, 0)	0 (0, 3.8)	−6.712[c]	**<0.001**	0 (0, 0)	3 (0, 9)
Aneurysm size, median[IQR], (mm)	5.2 (4.0, 7.0)	5.8 (3.8, 7.0)	−0.214[c]	0.830	5.3 (4.0, 7.3)	6.7 (4.7, 8.0)
Aneurysm location, *n* (%)			5.475[b]	0.140		
Anterior circulation	67 (36.8)	37 (48.7)			37 (38.9)	15 (45.5)
Internal carotid artery	81 (44.5)	25 (32.9)			38 (40.0)	13 (39.4)
Middle cerebral artery	17 (9.3)	4 (5.3)			11 (11.6)	2 (6.1)
Posterior circulation	17 (9.3)	10 (13.2)			9 (9.5)	3 (9.1)
Number of aneurysms, median[IQR]	1 (1, 1)	1 (1, 2)	−0.583[c]	0.560	1 (1, 1)	1 (1, 1)
Timing of interventional surgery, *n* (%)			2.661[b]	0.264		
0–3d	117 (64.3)	56 (73.7)			74 (77.9)	28 (84.8)
3–10d	50 (27.5)	17 (22.4)			17 (17.9)	4 (12.1)
>10d	15 (8.2)	3 (3.9)			4 (4.2)	1 (3.0)
Drainage methods, *n* (%)			16.298[b]	**<0.001**		
None	92 (50.5)	29 (38.2)			33 (34.7)	5 (15.2)
One type	88 (48.4)	38 (50.0)			60 (63.2)	24 (72.7)
Two or more types	2 (1.1)	9 (11.8)			2 (2.1)	4 (12.1)
Secondary cerebral infarction, *n* (%)	20 (11.0)	40 (52.6)	52.091[b]	**<0.001**	10 (10.5)	15 (45.5)
Rebleeding, *n* (%)	7 (3.8)	5 (6.6)	–	0.344	4 (4.2)	4 (12.1)
Pulmonary infection, *n* (%)	65 (35.7)	65 (85.5)	53.213[b]	**<0.001**	52 (54.7)	29 (87.9)
Hydrocephalus, *n* (%)	18 (9.9)	20 (26.3)	11.517[b]	**0.001**	12 (12.6)	10 (30.3)
Epilepsy, *n* (%)	13 (7.1)	11 (14.5)	3.415[b]	0.065	3 (3.2)	4 (12.1)
Cerebral hernia, *n* (%)	4 (2.2)	12 (15.8)	17.026[b]	**<0.001**	1 (1.1)	10 (30.3)
Cardiac event, *n* (%)	20 (11.0)	25 (32.9)	17.866[b]	**<0.001**	9 (9.5)	16 (48.5)

[a] is the *t*-value, [b] is the chi-square value, and [c] is the Z-value. The bold values mean the results of the univariate analysis in the modeling queue are statistically significant.

Discussion

With the continuous development of neurointerventional techniques and surgical materials, the clinical outcomes associated with endovascular treatment for aSAH have garnered increasing attention. A pivotal large-scale randomized clinical trial, the International Subarachnoid Aneurysm Trial (ISAT) (26), unequivocally demonstrated the superior clinical efficacy of endovascular coiling over traditional microsurgical clipping in the treatment of ruptured intracranial aneurysms. This therapeutic approach is increasingly gaining widespread adoption as a prominent tool for managing patients with aSAH, particularly among elderly individuals. Over recent years, neurosurgeons, both at the domestic and international levels, have endeavored to develop diverse prognostic models for subarachnoid hemorrhage, incorporating various influential factors. However, the majority of these models are hybrids, capable of predicting outcomes for both interventional embolization and clipping therapies. Models exclusively tailored for embolization are relatively scarce, and each of them exhibits distinct limitations. Therefore, our research has

developed a visual predictive model aimed at estimating the likelihood of adverse outcomes among aSAH patients 6 months following interventional embolization therapy. This model encompasses demographic data, clinical symptoms and admission consciousness scores, initial imaging assessments, in-hospital complications, and the first admission laboratory analyses. These variables are routinely encountered in clinical practice and easily accessible, rendering the model highly practical. The model's discrimination, calibration, and clinical utility have all been robustly validated, with satisfactory results from internal validation.

We also compared the derived nomogram with two well-established prognostic scoring systems widely employed in clinical practice, namely the WFNS and Hunt-Hess grading scales. Our findings revealed the AUC values of our nomogram were significantly higher than those of the two scoring systems, indicating that our nomogram can relatively accurately predict the prognosis of aSAH patients undergoing interventional embolization. The classical scoring scales showed poor predictive efficacy in our research data. We speculate that although the two classic scoring systems have been used for many years in the assessment of patient prognosis, different doctors may assign different GCS scores to the same patient, potentially leading to a certain degree of error. Moreover, the two scales have a limited role in predicting prognosis based only on clinical manifestations at admission, ignoring serious complications such as rebleeding, secondary cerebral infarction, cerebral herniation, and circulatory failure that may occur during the patient's hospitalization. In our modeling cohort of 76 patients with poor prognosis, 55 (72.3%) patients were admitted with a good Hunt-Hess classification, of whom 52 (94.5%) were comorbid with one or more complications, and 44 (57.9%) patients were admitted with a good WFNS classification, of whom 41 (93.2%) were comorbid with one or more complications. Similar results were observed in the validation cohort. To exemplify the strengths of our new prediction model, in

TABLE 4 Multivariate logistic regression analysis of poor prognosis for aSAH patients in the modeling cohort.

Variables	β	SE	*p*	OR (95%CI)
Age	0.082	0.020	<0.001	1.085 (1.044–1.128)
WFNS IV-V	1.321	0.561	0.018	3.746 (1.248–11.241)
mFisher 3–4	1.066	0.452	0.018	2.903 (1.198–7.035)
Secondary cerebral infarction	2.562	0.464	<0.001	12.966 (5.218–32.222)
Leukocyte counts on admission	0.282	0.071	<0.001	1.326 (1.153–1.525)
Goodness-of-fit test				
X^2				9.176
Degrees of freedom				8
p				0.328

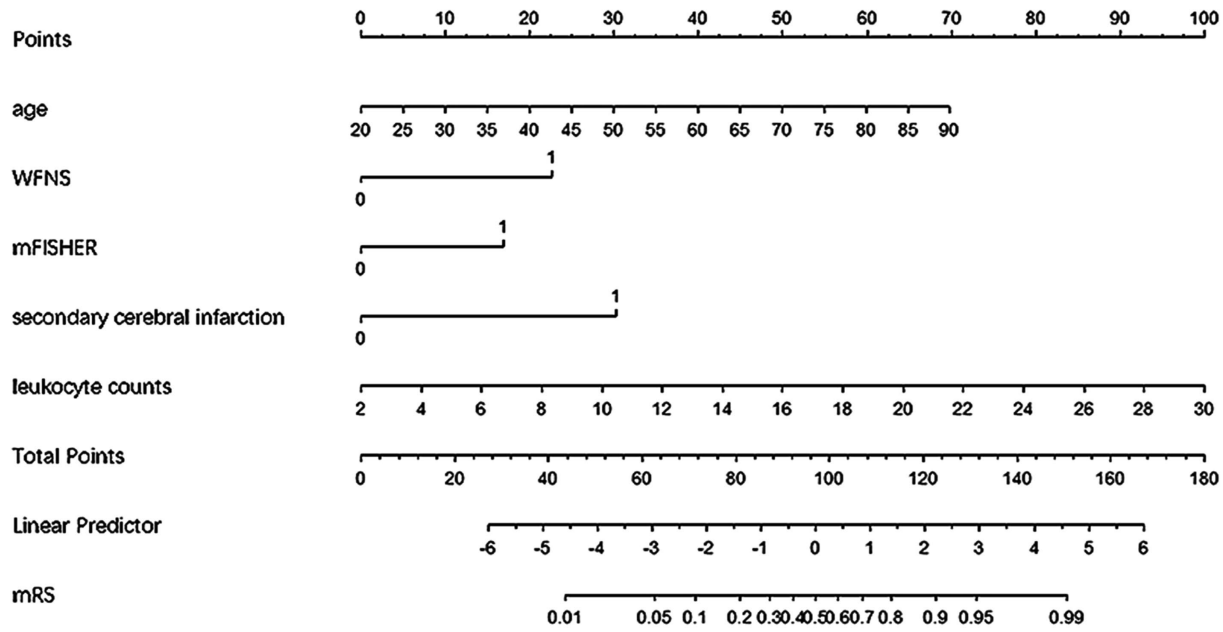

FIGURE 1
Nomogram for predicting poor prognosis in aSAH patients undergoing interventional embolization.

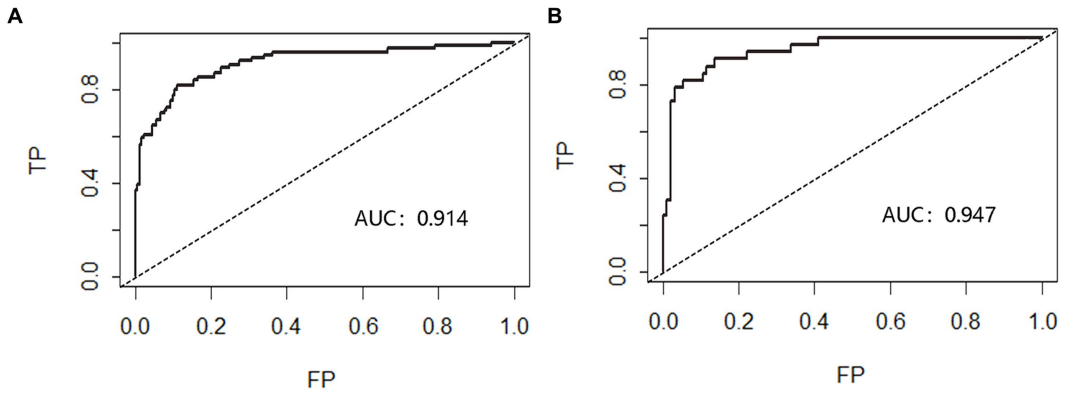

FIGURE 2
Receiver operating characteristic curve (ROC) validation of nomogram in aSAH patients. The risk prediction's true positive rate is represented by the Y-axis, while its false positive rate is represented by the X-axis. The nomogram's performance in the modeling queue **(A)** and validation queue **(B)** is shown by the black curve.

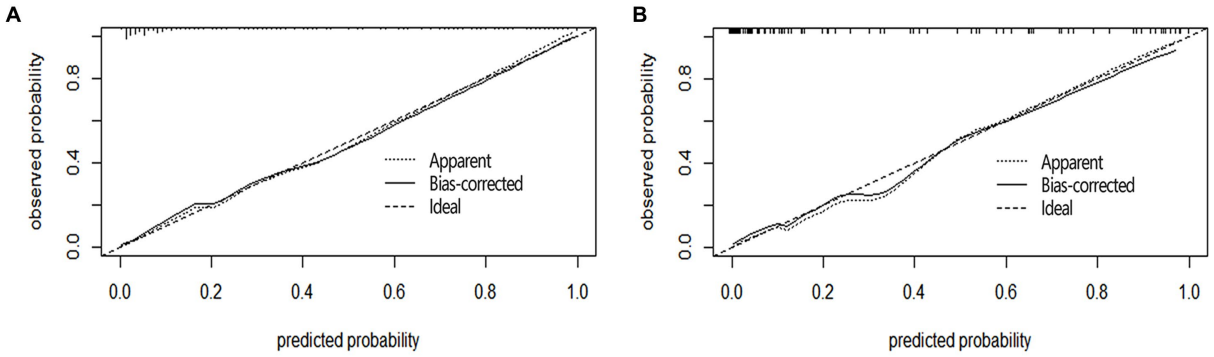

FIGURE 3
Calibration curves of nomogram in aSAH patients. The Y-axis represents the actual probability of poor prognosis in the aSAH patients, and the X-axis represents the predicted probability of poor prognosis in the aSAH patients. The diagonal dashed line, characterized by a slope of 1, symbolizes a flawless prediction from an ideal model. Meanwhile, the solid line depicts the prediction model's performance in both the modeling queue **(A)** and the validation queue **(B)**. The results show that the closer to the diagonal dashed line, the better the prediction.

addition to comparing it with other external rating scales, we also compared the prediction model with its constituent variables. The results reveal that the prediction performance of our model surpasses that of age, WFNS classification, mFisher score, secondary cerebral infarction, and the first white blood cell count upon admission.

Our study established age as an independent risk factor associated with unfavorable prognoses at the 6-month post-endovascular treatment in patients diagnosed with aSAH. Adverse outcomes were more common in the elderly cohort (age ≥ 60 years). Despite the many advantages of endovascular intervention, which has become an important treatment method for aSAH patients, older patients often experience higher perioperative complications, including subarachnoid clot formation and detachment, hydrocephalus, higher rebleeding rates, as well as pre-existing comorbidities such as diabetes, hypertension, and cardiopulmonary diseases (27). Although the definition of elderly individuals in the field of aSAH may vary among published articles, it is consistent with the outcomes of the International Subarachnoid Aneurysm Trial (26) that age is an inverse predictor of prognosis.

The current WFNS grading scale, introduced in 1988, is widely used for grading the severity and predicting the prognosis of aSAH. In our study, we also used the widely accepted WFNS grading scale. We categorized the WFNS grades into I-III and IV-V, aiming to avoid subtle distinctions between different grades while maximizing the differentiation between favorable and unfavorable outcomes in aSAH patients. The multivariate analysis also indicated that Patients with WFNS grades IV-V upon admission had a significantly increased chance of experiencing a poor outcome after 6 months following aSAH. This is consistent with previous research findings. Shen et al. (28) collected and analyzed data from 147 aSAH patients with poor prognosis, and their results suggested that WFNS grade V was an important predictive factor for poor prognosis. Furthermore, Li et al. (29) proposed a novel scoring model named "TAPS", utilizing Early Brain Injury (EBI) markers to forecast the functional outcomes of patients with aSAH at the 90-day time point. This model also included WFNS grades IV-V. Schuss et al. (30) also have affirmed that WFNS grade V stands out as a robust predictor of an adverse prognosis among individuals with aSAH. In general, the WFNS classification

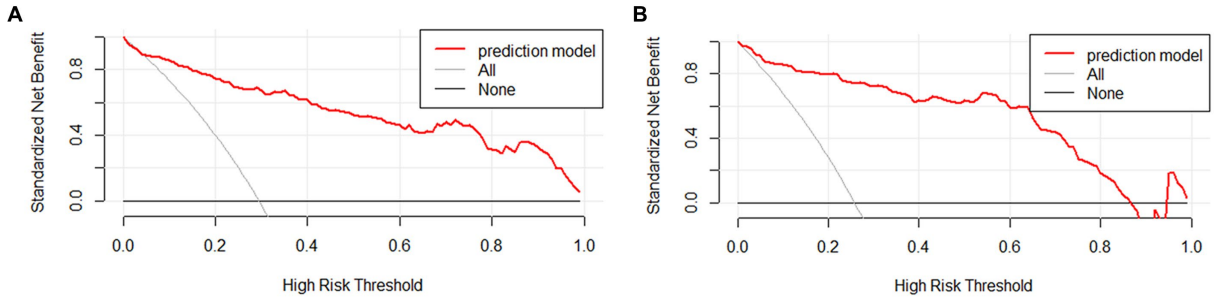

FIGURE 4
Clinical decision curves of nomogram in aSAH patients. The Y-axis illustrates the net benefit derived from the undertaken action, while the X-axis portrays the risk associated with an unfavorable prognosis. The slanted thin gray line represents the assumption that all patients take the intervention, the horizontal thick solid line represents that no patient takes the intervention, and the aSAH nomogram is depicted by the red curve in both the modeling queue **(A)** and the validation queue **(B)**.

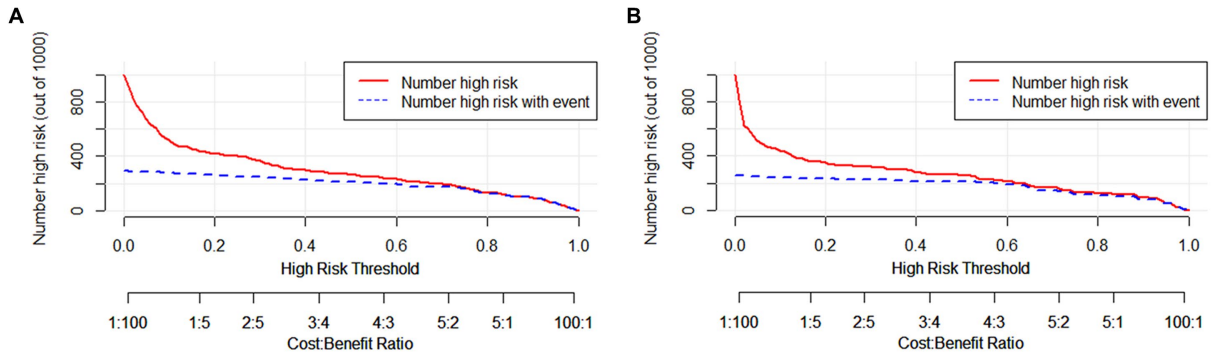

FIGURE 5
Clinical impact curves of nomogram in aSAH patients. The number of individuals the model identified as positive (high risk of poor prognosis) at each threshold probability is shown by the solid line, while the number of real positives at each threshold probability is shown by the dotted line. **(A)** From the modeling cohort, and **(B)** from the validation cohort.

TABLE 5 Comparison of the nomogram with WFNS and Hunt-Hess in the modeling group.

Comparison of different scales			Z/D	*p*
Nomogram	vs.	WFNS	6.618	<0.001
Nomogram	vs.	Hunt-Hess	8.577	<0.001
WFNS	vs.	Hunt-Hess	−2.180	0.029

can better respond to the neurological impairment of patients at the time of admission, indicating that the severity of neurological impairment in the early stage can determine the prognosis of patients to a certain extent, which is important for assessing the degree of risk of aSAH.

In our study, we also utilized the modified Fisher scoring system to assess the amount of subarachnoid hemorrhage. The modified Fisher score, introduced in 2006, emphasizes the presence of intraventricular hemorrhage (IVH) and the thickness of blood in the cisterns. Compared to the original Fisher score, the modified version provides a more accurate prediction of symptomatic vasospasm after aSAH and demonstrates superior in predicting the occurrence of new cerebral infarctions and patient outcomes. A study (13) based on a cohort of 271 aSAH patients aimed to analyze the relationship between the increase in various scores (Fisher, modified Fisher, and Claassen scale) assessed from patients' admission CT scans and the risk of subsequent complications. The results revealed that, compared to Fisher and Claassen scales, the relationship between an increase in the modified Fisher score and the incidence of complications was more linear. Within this scoring system, each additional point was linked to a heightened likelihood of experiencing vasospasm, delayed cerebral infarction, and an unfavorable prognosis. The study conducted by Oliveira et al. (14) also discovered that the Fisher Revised Scale (FRS) may be more effective in identifying patients at risk of clinical vasospasm and neurological deterioration. Similarly, in our study, the modeling cohort had 25.2% of patients with severe imaging manifestations (mFisher score 3–4), of which 58.5% had a poor prognosis. The heavier the patient's imaging score, the worse the prognosis, and the difference was statistically significant ($p < 0.001$). The potential explanation lies in the sudden surge of intracranial pressure after the rupture of an arterial aneurysm. This event triggers a decline in cerebral perfusion pressure and compromises the autoregulatory function, which may ultimately lead to transient or persistent ischemia. The volume of blood entering the subarachnoid space correlates with the peak ICP at the moment of aneurysm rupture, according to the Monro-Kellie doctrine. The substantial correlations between the imaging results of individuals with aSAH and

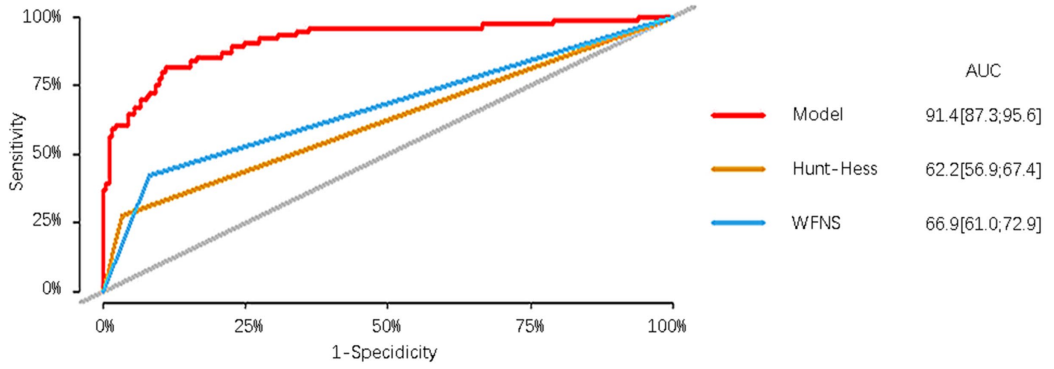

FIGURE 6
Comparison of the nomogram with WFNS and Hunt-Hess.

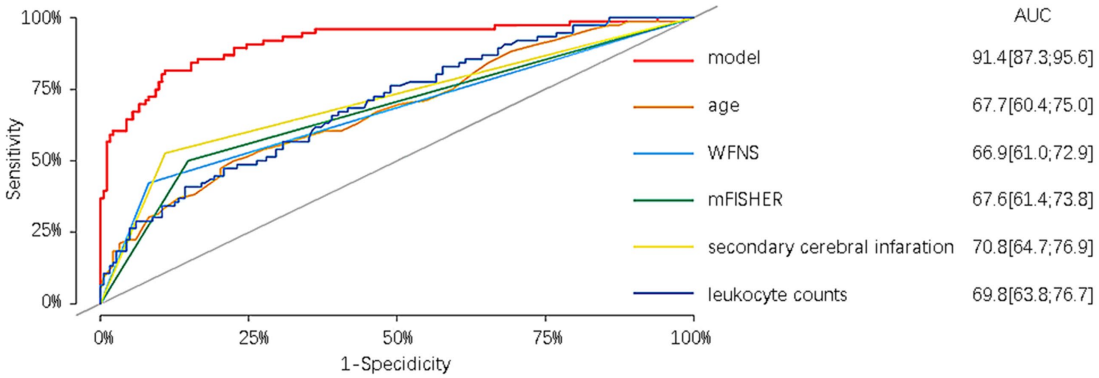

FIGURE 7
Comparison of the nomogram with its component variables.

the initial clinical presentation and prognosis can be explained by this relationship between the burden of intracranial hemorrhage and the severity of early brain injury (31, 32). However, it is worth noting that relying solely on clinical grading or radiological scoring to assess the prognosis of aSAH may result in significant deviations in predicting patient outcomes.

There is no doubt that post morbidity complications have a significant impact on the adverse prognosis of individuals with aSAH. Our study collected relevant data on post-illness complications such as cerebral infarction, rebleeding, lung infection, hydrocephalus, seizures, brain herniation, and cardiovascular events for all included patients. The final results also demonstrated fair predictive efficacy of secondary cerebral infarction on the 6-month prognosis of patients undergoing interventional embolization therapy, with an AUC value of 0.708 (95%CI = 0.647–0.769). The reasons for this may be related to the initiation of cell death mechanisms, disruption of the blood–brain barrier, and acute inflammatory responses during the acute phase of SAH. All of these factors could contribute to the occurrence of brain edema, which itself is a factor influencing prognosis. Additionally, acute hemodynamic instability may lead to microvascular spasm, microthrombus formation, and failure of cerebral autoregulation. All of these factors may be involved in the sustained ischemic injury following SAH and result in delayed manifestations (33). The impact of cerebral infarction on the prognosis of SAH is supported by several key findings. Vergouwen et al. (34) suggested that independent of angiographic vasospasm, cerebral infarction has a direct influence on prognosis, making it an important research target for improving SAH outcomes. Taki et al. (35) reported that factors including cerebral infarction induced by both endovascular coiling and vasospasm significantly affect adverse outcomes. Kanamaru et al. (36) demonstrated that cerebral infarction, regardless of its underlying cause, significantly influences the poor prognosis after SAH, and cerebral vasospasm remains the most crucial potential breakthrough for treatment. In a study by Su et al. (37), they also found that the short-term prognosis of aSAH hospitalized patients in the cerebral infarction group was significantly worse than that of the non-cerebral infarction group, and that the patients' degree of cognitive and sensorymotor impairment usually determines the length of hospitalization, which could explain why the average length of hospitalization in the group of cerebral infarcted patients was longer and the outcome was poorer.

In our study, secondary cerebral infarction is not directly equivalent to aneurysm embolization itself, but rather associated with potential complications (such as vasospasm or delayed cerebral ischemia) that may occur after the onset of the disease. Although our study did not further differentiate the specific cases of cerebral infarction after subarachnoid hemorrhage. However, regardless of the

mechanism, cerebral infarction is the ultimate manifestation of various pathways of neurologic injury, all of which significantly contribute to the poor prognosis of SAH. In addition most studies tend to exclude cerebral infarctions due to medical factors or medical decision-making factors, which equally have an impact on prognostic prediction. The data from our study, which included all cases of cerebral infarction occurring after aSAH, confirmed that there was a notable disparity in secondary cerebral infarction rates between the groups with good and poor prognosis. It has been recognized as a distinct risk factor independently associated with an adverse prognosis at the 6-month follow-up in patients undergoing interventional treatments. The prediction model we constructed included relevant complication variables, which may help improve the sensitivity in predicting adverse events.

Our nomogram also emphasizes the importance of preoperative inflammatory biomarkers, further highlighting the significance of neurogenic inflammatory response during the onset of aSAH. This could be because uncontrolled inflammation occurs after early brain injury as a result of extravascular blood response, decreased brain autoregulation, product release from injured brain tissue, and ischemia–reperfusion injury. Extracellular vesicles formed from astrocytes are released in response to pro-inflammatory cytokines like interleukin-1β (IL-1β). These vesicles penetrate the peripheral circulation and facilitate leukocyte migration towards the central nervous system. When peripheral leukocytes move into the brain and cerebrospinal fluid, active neutrophils cause damage to cerebral microvessels, worsening the effects of ischemia injury. The severe inflammatory response within the system that follows SAH peaks in 24 to 48 h and causes a delay in the deterioration of the nervous system (38).

Studies by Mahta et al. (39), Muroi et al. (40), and Srinivasan et al. (41) have all demonstrated that the early inflammatory response occupies a significant position in the pathophysiology of SAH. In our study, there appeared to be a mild elevation in the white blood cell count upon admission, which is a relatively common finding in the early stages following SAH. We also observed that leukocyte counts tended to be higher in patients with aSAH who had a poor prognosis at 6 months, and the observed elevation in leukocyte counts reached statistical significance. While the high proportion of infectious complications in patients with poor prognosis may be an expected fact influencing white blood cell count, our study included patients within 72 h of the onset of illness, and the elevation in leukocyte counts at admission monitoring mostly preceded the occurrence of infectious complications.

Furthermore, another negative consequence of the inflammatory response following SAH may be the impairment of organ functions, which can have varying degrees of impact on prognosis. Researchers have observed that the systemic inflammatory response after aSAH may play a role in cardiac dysfunction, as their studies have revealed an independent correlation between elevated total leukocytes and neutrophils and cardiac injury in aSAH patients (42). Likewise, the occurrence of systemic inflammatory response syndrome might result in the progression of acute lung injury (43). In the practical work of clinical physicians, the blood routine examination in aSAH patients upon admission may serve as a simple method to help assess the potential for an adverse prognosis in patients.

This study has several limitations, firstly, we used a retrospective collection of statistical data. Secondly, when assessing functional neurological outcomes, we intentionally set the follow-up point at 6 months post-discharge, recognizing it as a crucial period for neurological recovery. However, it would have been more accurate to obtain data for long-term follow-up. In addition, although the study data were obtained from different centers, the two centers were closely related, with varying degrees of sharing in terms of medical technology, staffing, and means of patient care, which may have led to unavoidable bias in the analyses and conclusions. Further external validation of the nomogram in larger multicentre studies is required.

Conclusion

The nomogram we constructed includes five variables: age, WFNS grades of IV-V, mFisher score of 3–4, secondary cerebral infarction and the first leukocyte counts on admission, which can early and effectively predict the 6-month prognosis of patients with aSAH who underwent interventional embolization, with good differentiation, calibration and clinical applicability. The model allows for a relatively accurate assessment of patients' prognosis in the early stages of the disease, providing reliable evidence-based medicine to assist doctors in taking necessary intervention measures for high-risk patients as early as possible.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Fujian Provincial Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QG: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. HC: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization. SL: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. ZG: Writing – review & editing, Validation, Software, Resources, Project administration, Investigation, Funding acquisition, Formal analysis. ZS: Writing – original draft, Validation, Software, Investigation, Formal analysis, Data curation. FC: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1410735/full#supplementary-material

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The association between dexterity and upper limb impairment during stroke recovery

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Introduction: Stroke-induced upper limb disabilities can be characterized by both motor impairments and activity limitations, commonly assessed using Fugl-Meyer Motor Assessment for Upper Extremity (FMMA-UE) and Action Research Arm Test (ARAT), respectively. The relationship between the two assessments during recovery is largely unstudied. Expectedly they diverge over time when recovery of impairment (restitution) plateaus, but compensation-driven improvements still occur. The objective of this study is to evaluate the alignment between FMMA-UE and ARAT in defining upper limb functional recovery categories by ARAT scores. We aimed to establish cut-off scores for both measures from the acute/early subacute, subacute and chronic stages of stroke recovery.

Methods: Secondary analysis of four prospective cohort studies (acute/early subacute: $n = 133$, subacute: $n = 113$, chronic: $n = 92$) stages post-stroke. Receiver operating characteristic curves calculated the area under the curve (AUC) to establish optimal FMMA-UE cut-offs based on predefined ARAT thresholds distinguishing five activity levels from no activity to full activity. Weighted kappa was used to determine agreement between the two assessments. We used minimally clinically important difference (MCID) and minimal detectable change (MDC_{95}) for comparison.

Results: FMMA-UE and ARAT scores showed no relevant divergence across all recovery stages. Results indicated similar cut-off scores in all recovery stages with variability below MCID and MDC_{95} levels. Cut-off scores demonstrated robust AUC values from 0.77 to 0.86 at every recovery stage. Only in highly functional patients at the chronic stage, we found a reduced specificity of 0.55. At all other times sensitivity ranged between 0.68 and 0.99 and specificity between 0.71 and 0.99. Weighted kappa at the acute/early subacute, subacute and chronic stages was 0.76, 0.83, and 0.81, respectively.

Discussion: Our research shows a strong alignment between FMMA-UE and ARAT cut-off scores throughout stroke recovery, except among the subgroup of highly recovered patients at the chronic stage. Discrepancies in specificity potentially stem from fine motor deficits affecting dexterity outcomes that are not captured by FMMA-UE. Additionally, the high congruence of both measures suggests they are not suited to distinguish between restitution and

compensation. Calling for more comprehensive assessment methods to better understand upper limb functionality in rehabilitation.

KEYWORDS

rehabilitation, stroke, upper limb, outcome measures, Fugl-Meyer motor assessment, Action Research Arm Test

1 Introduction

Upper limb motor impairments typically reflect deficits in basic body functions, such as the ability to open and close one's hand, while activity limitations pertain to difficulties in performing daily tasks like drinking from a cup or dressing oneself (1). These two dimensions, although interconnected, do not exhibit a linear relationship between them, suggesting a nuanced relationship between physical impairments and their practical implications during recovery (2–5).

To measure upper limb impairment and activity deficits post-stroke, both the Fugl-Meyer Motor Assessment for Upper Extremity (FMMA-UE) and the Action Research Arm Test (ARAT) have been endorsed by the Stroke Recovery and Rehabilitation Roundtable (SRRR) task force, the European Stroke Organization (ESO) and other international working groups for assessing motor recovery and the quality of rehabilitation (5–8). These high-level recommendations acknowledge FMMA-UE and ARAT as reliable and valid tools for assessing upper limb disability (8–10). The FMMA-UE is designed to capture typical stroke-induced motor impairments, focusing on aspects such as reflexes, coordination, and the ability to move in and out of synergy patterns or produce fractionated movements (11). In contrast, ARAT intends to assess activity limitations in arm usage related to grasping, gripping, and object manipulation (6, 12). Consistency in item response, stability over time and the presence of floor and ceiling effects have been investigated extensively (13–16). However, practical considerations often lead clinical trials to choose either FMMA-UE or ARAT (5). Interestingly, this preference can vary significantly by region, affecting the translatability of trial results (17–20). Additionally, constraints such as patient availability, the need for trained personnel, and cost-effectiveness currently limit the ability of clinical practices to implement both measures outside of research settings.

Therefore, understanding how the results of one domain's outcome measure might correspond to the context of the other domain remains an intriguing question. Recently, Hoonhorst et al. attempted to delineate this relationship by establishing cut-off scores for FMMA-UE that correspond to clinical ARAT classifications of activity levels (21). They found a high sensitivity and specificity as well as overall agreement for both assessments in five capacity categories. However, their findings were confined to cross-sectional analyses of patients in chronic stages, thereby leaving a substantial gap in our comprehension of this relationship across the entire spectrum of post-stroke recovery. Such understanding is crucial, given the distinct patterns of recovery observed in impairment and activity, as well as the unique aspects of upper limb motor function captured by each assessment tool.

Recovery of impairment, known as true restitution, and recovery of activity exhibit distinct trajectories throughout the post-stroke rehabilitation process (22). Restitution, primarily observed in the initial weeks and months following a stroke, tends to plateau during the subacute stage (23). In contrast, improvements in activity levels can be mediated by compensatory strategies, enabling changes even in the chronic stages after stroke. This divergence suggests that while the restoration of motor function may stabilize relatively early, functional gains in daily activities can continue over a longer period.

Moreover, the assessments of upper limb impairment provided by FMMA-UE and ARAT may not capture all aspects equally. For instance, FMMA-UE subtasks offer only a partial representation of fine motor control, whereas such control significantly influences ARAT outcomes (24). Similarly, while the presence of synergistic movements is not directly evaluated in ARAT scores (12, 25, 26), these movements are assessed with the FMMA-UE. This underscores the importance of considering longitudinal changes in both measures, for better translatability between domains.

Our aim was to evaluate the alignment between FMMA-UE and ARAT in defining upper limb functional recovery categories defined by ARAT scores. We aimed to establish cut-off scores to achieve this alignment by establishing cut-off scores for both outcome measures from the acute/early subacute to the chronic stages of stroke recovery. Specifically, we assessed the agreement of these FMMA-UE thresholds with ARAT's activity categories—none, poor, limited, notable, and full. We hypothesized a divergence in assessment scores over time, with an initial close alignment between FMMA-UE and ARAT, with both being driven mainly by restitution, and a progressively widening gap as recovery transitions beyond the subacute stage mainly driven by compensation, thus primarily influencing ARAT scores.

2 Materials and methods

2.1 Study design

We conducted a secondary analysis of existing data pooled from four prospective cohort studies, including one dataset from a rehabilitation inpatient clinic. We selected data at three different stages of recovery: acute/early subacute (2 weeks ± 14), subacute (3–6 months ± 14), and chronic (>6 months) stage post-stroke (27).

Ethical approval from the cantonal ethics committee Zurich and Northwest and Central Switzerland was obtained before study start

Abbreviations: ARAT, Action Research Arm Test; AUC, Area under the curve; ESO, European Stroke Organization; FMMA-UE, Fugl-Meyer Motor Assessment for Upper Extremity; ICF, International Classification of Functioning, Disability and Health; ISSRA, International Stroke Recovery and Rehabilitation Alliance; MCID, Minimally Clinically Important Difference; MDC, Minimal Detectable Change; NIHSS, National Institutes of Health Stroke Scale; ROC, Receiver operating characteristic; SRRR, Stroke Recovery and Rehabilitation Roundtable.

and adhered to the ethical standards of the revised Declaration of Helsinki. The studies were registered prospectively with their respective BASEC identifiers in Cohort 2 (2017–00948), Cohort 3 (2017–01070), and Cohort 4 (2017–00889). These studies were also registered on ClinicalTrials.gov with the identifiers NCT03294187, NCT03522519, and NCT03287739. All participants or their next of kin provided written informed consent. Secondary data analysis for the cohort 2, 3 and 4 was approved by the cantonal ethics committee Zurich (Business Administrator System for Ethics Committee identifier 2020–00218). Participants from Cohort 1, drawn from a Swiss clinical dataset, cereneo Schweiz AG, consented to further data analysis under the clinic's general consent agreement (see Supplementary Figure S1). Reporting is adherent to the STROBE reporting guidelines (see Supplementary Table S1) (28).

2.2 Study population

The sample comprised stroke patients with a first-ever unilateral ischemic or hemorrhagic stroke, who were recruited at the acute/early subacute, subacute, or chronic stage, were 18 years or older, and had an upper limb motor deficit at the acute stage. Inclusion was based on either FMMA-UE, ARAT or National Institutes of Health Stroke Scale (NIHSS) arm score ≥ 1 motor scores. Participants were excluded if they had a neurological or other disease affecting the upper limb before the stroke, known or suspected non-compliance, drug or alcohol abuse. Patients underwent medical and rehabilitation therapies following Swiss national standards (29). More detailed information regarding specific inclusion and exclusion criteria is provided in the Supplementary material (30–32).

2.3 Outcome measures

The FMMA-UE and the ARAT are both recommended outcomes for evaluating upper limb deficits in the International Classification of Functioning, Disability and Health (ICF) body function and activities domain respectively, following International Stroke Recovery and Rehabilitation Alliance (ISSRA) recommendations (1, 5, 7, 8).

2.3.1 Fugl-Meyer motor assessment for upper extremity

The FMMA-UE measures capacity-based impairment in stroke patients. It evaluates movement, coordination, and reflexes in the upper limb using 33 items based on Twitchell and Brunnstrom's motor recovery phases (33, 34). Higher scores on the 3-point scale indicate more robust motor function, where 0 = cannot perform; 1 = performs partially; and 2 = performs fully, with a maximal total score of 66 points (see Supplementary material) (11).

2.3.2 Action Research Arm Test

The ARAT is an observational measure with 19 items that assess upper limb activity by evaluating the ability to handle objects of different sizes, shapes, and weights to complete activities of daily living tasks. Each item is on a 4-point ordinal scale (0 = unable; 1 = partial; 2 = abnormal; 3 = normal), divided into 4 domains (i.e., grasp., grip, pinch, and gross movement). The maximum score is 57 points, indicating full upper limb activity and the minimum is zero, indicating no upper limb activity (see Supplementary material). The ARAT equipment kit used was the same as in the original article proposed by Lyle (35), and we followed the standardized methodology for conduction and scoring by Yozbatiran (12).

Building upon previous research (21, 36–38), upper limb activity was classified into five distinct categories to allow for comparison with the predefined ICF levels of regained motor function. These categories range from "no activity" (ARAT 0 to 10 points, indicating complete activity limitation according to the ICF) to "full activity" (ARAT 55 to 57 points, indicating no activity limitation and near full recovery). The other categories include "poor activity" (ARAT 11 to 21 points, severe activity limitation), "limited activity" (ARAT 22 to 42 points, moderate activity limitation), and "notable activity" (ARAT 43 to 54 points, mild activity limitation).

2.4 Data collection

ARAT and FMMA-UE were administered by trained practitioner-researchers using a standardized protocol (12, 39). Study visits occurred during in-patient hospitalization. After discharge, the patient was evaluated during an out-patient visit or at home (30–32).

2.5 Data analysis

Clinical and demographic characteristics were analyzed using descriptive and nonparametric inference statistics (median, interquartile and frequencies) suited to our data distribution. The Kruskal-Wallis test was utilized to analyze ordinal and continuous variables across multiple independent groups, making it ideal for assessing quantitative data that do not follow a normal distribution. Additionally, the Pearson chi-square test was used to analyze differences in nominal variables, which is ideal for testing the independence of categorical data.

To identify optimal FMMA-UE cut-off scores for the five distinct activity categories of the ARAT, we computed receiver operating characteristic (ROC) curves at each stage of stroke recovery for each group separately (acute/early subacute, subacute, chronic) (21, 37). The optimum area under the curve (AUC) in terms of sensitivity and 1-specificity was then identified, and ROC coordinate points were used to select the best threshold based on the maximum sensitivity and 1-specificity (40). For sensitivity and specificity, a test performing below 0.7 is considered unreliable, while a range of 0.7 to 0.9 is considered good, and above 0.9 is excellent (41). To evaluate a test's accuracy in identifying both false positives and false negatives, the sum of sensitivity and specificity serves as a useful guideline. High-quality testing requires that this combined score is at least 1.5, indicating higher accuracy. A score of 1 renders the test meaningless, while a score of 2 represents a perfect test. Weighted kappa was determined to measure the agreement between the FMMA-UE observations within the five ARAT subcategories (42). Kappa values were interpreted as follows: poor ($k = 0$–0.40), fair ($k = 0.41$–0.75), or excellent ($k = 0.76$–1) (43). We analyzed the differences of FMMA-UE cut-off scores across acute/early subacute, subacute, and chronic stroke recovery groups between our and previously reported results, using established clinically meaningful differences as a reference. These were defined as 13 points for acute/early subacute (44), 9 points

TABLE 1 Patients' characteristics.

Patients' characteristics	Acute/Early subacute (*N* = 133) C1, *n* = 30 C2, *n* = 0 C3, *n* = 88 C4, *n* = 15	Subacute (*N* = 113) C1, *n* = 9 C2, *n* = 2 C3, *n* = 84 C4, *n* = 18	Chronic (*N* = 92) C1, *n* = 7 C2, *n* = 42 C3, *n* = 43 C4, *n* = 0	*p*-value
Sex, male/female*	80/53	64/49	54/38	0.86
Age, years†	68.8 ± 14.9	71.4 ± 13	68 ± 12.3	0.07
Limb affected side Left, right	80/53	66/47	55/37	0.96
ARAT total score‡	32(0–44)	38(17–55)	39(15–55)	0.001
FMMA-UE total score‡	37(13–50)	44(27–56)	41(24–54)	0.006
Upper limb activity categories	Patient *N* = 133	Patient *N* = 113	Patient *N* = 92	0.13
No (ARAT score 0–10)	46	24	20	
Poor (ARAT score 11–21)	9	6	7	
Limited (ARAT score 22–42)	40	33	30	
Notable (ARAT score 43–54)	19	21	11	
Full (ARAT score 55–57)	19	29	24	

Baseline characteristics of all the patients included in the study. Values are *n, †mean ± SD, or ‡median (interquartile range). ARAT (Action Research Arm Test). FMMA-UE (Fugl-Meyer motor assessment for upper extremity). C1 = Cohort 1, C2 = Cohort 2, C3 = Cohort 3, C4 = Cohort 4.

for subacute (45), and 5.3 points for chronic stages (46), based on established Minimally Clinically Important Difference (MCID) values. Additionally, we used established values for Minimal Detectable Change (MDC) at a 95% confidence level (MDC_{95}) as the minimal difference which could be explained by random variability in the measurements (47). The different cut-off scores across functional recovery categories and chronic stages were compared against these change indicators; only differences exceeding these thresholds were considered relevant.

RStudio software with R version 4.0.3 and IBM® SPSS® Statistics 29 were used for the statistical analyses, and the level of statistical significance was set to <0.05 (48).

3 Results

We analyzed data concerning upper limb deficits in patients evaluated with the FMMA-UE and ARAT across the three distinct stages of post-stroke recovery. The acute/early subacute stage included patients assessed within two weeks, plus or minus fourteen days, post-stroke ($n = 133$), where the median assessment time was 9 days (range: 6–30 days). The subacute stage encompassed assessments from 2 weeks before 3 months up to 6 months post-stroke ($n = 113$), with a median assessment time of 93 days (range: 76–163 days). The chronic stage involved patients assessed beyond 6 months post-stroke ($n = 92$), with a median assessment time of 375 days (range: 182–4,850 days). See Table 1 for further patient characteristics. No significant difference was observed in sex, age, limb affected side and distribution of upper limb activity categories, as revealed by Pearson chi-square test or Kruskal-Wallis test. However, a significant difference in ARAT and FMMA-UE total scores, as revealed by the Kruskal-Wallis test, was found between recovery stages, with chronic patients having higher scores than acute/early subacute patients.

Optimal FMMA-UE cut-off scores based on five distinct ARAT activity categories across acute/early subacute, subacute, and chronic stages post-stroke are shown in Table 2. The first row shows ARAT scores for its five recovery categories. Second to Fourth rows show the computed optimal cut-offs for FMMA-UE.

We compared the results from Hoonhorst et al. on chronic patients to our results. Both results are listed side by side in Table 2 (21). The differences between the FMMA-UE scores defining different activity categories in their study compared to ours ranged from 0 to 3 points across all activity categories at the chronic stage. These differences are below the MCID threshold of 13 points, indicating that they were not clinically relevant. Furthermore, these differences were smaller than the MDC in upper extremity FMMA-UE (MDC_{95}) of 5.3 points (44, 46, 47).

We observed only small differences in the FMMA-UE cut-off scores within each upper limb activity category (Table 2). These differences were below the MCID and MDC_{95} threshold, indicating there were clinically insignificant. No Activity: Scores consistently ranged from 0–19 across all stages. Poor Activity: Scores slightly decreased from 20–32 at the acute/early subacute stage to 20–30 at the subacute stage and further to 20–28 at the chronic stage. Limited Activity: Scores varied from 33–47 at the acute/early subacute stage, to 31–47 at the subacute, slightly reduced to 29–45 at the chronic stage. Notable Activity: Scores decreased from 48–57 at the acute/early subacute stage to 48–55 at the subacute and narrowed further to 46–53 at the chronic stage. Full Activity: Scores changed from 58–66 at the acute/early subacute stage to 56–66 at the subacute and adjusted down to 54–66 at the chronic stage.

Table 3 presents the optimal FMMA-UE cut-off scores based on five distinct ARAT activity categories at the acute/early subacute, subacute, and chronic stage post-stroke alongside their corresponding Sensitivity, Specificity and AUC values. At the acute/early subacute stage, AUC ranged from 0.77 (95% confidence interval CI, 0.61–0.93; $p < 0.004$) to 0.92 (95% CI, 0.84–1; $p < 0.000$). At the subacute stage AUC ranged from 0.86 (95% CI, 0.75–0.97; $p < 0.0001$) to 0.94 (95% CI, 0.89–1; $p < 0.0001$). At the chronic stage, AUCs ranged from 0.74 (95%

CI.57–1; $p < 0.024$) to 0.93 (CI, 0.83–1; $p < 0.001$). The data in Table 3 demonstrates that the optimal FMMA-UE cut-off scores provide robust diagnostic performance across all stages of post-stroke recovery, evidenced by high sensitivity and specificity values, indicating high accuracy with a low rate of false negatives and positives. An exception to this robust diagnostic performance can be seen at the chronic stage between the categories 'notable' versus 'full', where specificity was 0.55 and the sum of sensitivity and specificity was 1.38.

Each cell in Table 4 displays the percentage of patients classified from no activity to full activity by both assessments. Green highlighting indicates a congruent classification between the ARAT activity category and the FMMA-UE activity category. A one-category disagreement, such as from No to Poor or from Notable to Full, results in a yellow highlight. A two-category disagreement is highlighted in red.

Table 4 displays a heatmap of activity categories agreement between the ARAT and FMMA-UE scores, at the acute/early subacute stage, perfect agreement (matrix diagonal highlighted in green) accounted for 65.5% of patients, while 4.6% presented major disagreement. At the subacute stage, perfect agreement accounted for 74.3% of patients, and major disagreement occurred in 1.8%. At the chronic stage, perfect agreement accounted for 72.7%, while major disagreement occurred in 7.6%.

The agreement between the five ARAT upper limb activity categories and the associated FMMA-UE scores demonstrated excellent consistency, as evidenced by high weighted kappa results at all stages: Acute/early subacute: weighted $k = 0.76$; 95% CI, 0.69–0.82, Subacute: weighted $k = 0.83$; 95% CI, 0.77–0.89 and Chronic: weighted $k = 0.81$; 95% CI, 0.74–0.88.

TABLE 2 Optimal FMMA-UE cut-off scores based on five distinct ARAT activity categories across acute/early subacute, subacute, and chronic stages post-stroke.

Upper limb					
Activity category / Assessment	No	Poor	Limited	Notable	Full
ARAT	0–10	11–21	22–42	43–54	55–57
FMMA-UE					
Acute/early subacute stage	0–19	20–32	33–47	48–57	58–66
Subacute stage	0–19	20–30	31–47	48–55	56–66
Chronic stage	0–19	20–28	29–45	46–53	54–66
Chronic stage (Hoonhorst et al)*	0–22	23–31	32–47	48–52	53–66

*Results from Hoonhorst and colleagues for comparison (21).

4 Discussion

Our study aimed to systematically evaluate the alignment between FMMA-UE and ARAT in defining upper limb functional recovery categories across different stages of stroke recovery. We anticipated that the congruence between FMMA-UE and ARAT cut-off scores would vary throughout the recovery process. To explore this hypothesis, we built upon the work of Hoonhorst et al. (21), who investigated a similar relationship but focused on the chronic stage of stroke recovery. In contrast, our study sought to extend this analysis across acute/early subacute, subacute, and chronic stages.

Our findings revealed highly corresponding cut-off scores for the FMMA-UE in relation to upper limb activity categories across all stages of stroke recovery. The differences observed remained within a narrow range, not exceeding established MCID values, which range from 5.3 for chronic to 13 for acute/early subacute stroke patients (44, 46), and an MDC_{95} of 5.2 (47). The overall fit of cut-off scores, reflected in high sensitivity, specificity, and AUC values across all stroke stages, indicates that motor scores achieved on the FMMA-UE are highly associated with the measured activity categories following the ARAT throughout recovery.

As mentioned above, both the ARAT and FMMA-UE are widely used assessments of upper limb function after stroke, measuring

TABLE 3 Sensitivity, specificity and area under curve for the computed cut-off scores.

	Activity category	ARAT cut-off	FMMA-UE cut-off	Sens	Spec	Sens + Spec	AUC	AUC 95% CI	*p*-value
Acute/early subacute stage	No *vs* Poor	10	19	0.78	0.87	1.65	0.87	0.77–0.99	<0.0001
	Poor *vs* limited	21	32	0.70	0.99	1.69	0.92	0.84–1	<0.0001
	Limited *vs* Notable	43	47	0.79	0.80	1.59	0.87	0.79–0.96	<0.0001
	Notable *vs* Full	55	58	0.68	0.84	1.52	0.77	0.61–0.93	0.004
Subacute stage	No *vs* Poor	10	19	0.99	0.83	1.82	0.91	0.81–1	0.002
	Poor *vs* limited	21	30	0.82	0.99	1.81	0.91	0.82–1	0.002
	Limited *vs* Notable	43	47	0.86	0.91	1.77	0.94	0.89–1	<0.0001
	Notable *vs* Full	55	56	0.83	0.81	1.64	0.86	0.75–0.97	<0.0001
Chronic stage	No *vs* Poor	10	19	0.99	0.85	1.84	0.93	0.83–1	0.001
	Poor *vs* limited	21	28	0.90	0.71	1.61	0.86	0.71–1	0.003
	Limited *vs* Notable	43	45	0.91	0.80	1.71	0.91	0.80–1	<0.0001
	Notable *vs* Full	55	54	0.83	0.55	1.38	0.74	0.57–1	0.024

The ARAT is scored from 0 to 57 points, and the FMMA-UE is scored from 0 to 66. No activity, ARAT 0 to 10 points; Poor activity, ARAT 11 to 21 points; Limited activity, ARAT 22 to 42 points; Notable activity, ARAT 43 to 54 points; Full activity, ARAT ≥ 55 points. Sens., sensitivity; Spec., specificity; AUC, Area under the curve; CI, confidence interval.

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TABLE 4 ARAT and FMMA-UE categories agreement at acute/early subacute, subacute and chronic stage post-stroke.

		Activity category	FMMA-UE					
			No (%)	Poor (%)	Limited (%)	Notable (%)	Full (%)	Total (%)
ARAT	Acute/Early subacute	No (%)	27.1	6	1.5	0	0	34.6
		Poor (%)	1.5	5.3	0	0	0	6.8
		Limited (%)	0.8	8.3	15	4.5	1.5	30.1
		Notable (%)	0	0	3	8.3	3	14.3
		Full (%)	0	0	0.8	3.8	9.8	14.3
		Total (%)	29.3	19.5	20.3	16.5	14.3	100
	Subacute	No (%)	17.7	2.7	0.9	0	0	21.2
		Poor (%)	0	5.3	0	0	0	5.3
		Limited (%)	0	8	18.6	2.7	0	29.2
		Notable (%)	0	0	2.7	9.7	6.2	18.6
		Full (%)	0	0	0.9	1.8	23	25.7
		Total (%)	17.7	15.9	23	14.2	29.2	100
	Chronic	No (%)	18.5	3.3	0	0	0	21.7
		Poor (%)	0	5.4	2.2	0	0	7.6
		Limited (%)	0	4.3	22.8	4.3	5.4	32.6
		Notable (%)	0	0	2.2	4.3	5.4	12
		Full (%)	0	0	2.2	2.2	21.7	26.1
		Total (%)	18.5	13	29.3	10.9	28.3	100

Heatmap of activity categories agreement between the ARAT and FMMA-UE scores. Each cell displays the percentage of patients classified from no activity to full activity by both assessments. Green highlighting indicates the matrix diagonal, where both scores agree. Disagreements are highlighted in yellow (discrepancy in one category) or red (discrepancy in two categories).

different aspects of disability. Current research underscores the difficulty of comparing studies using different scoring systems (4), and recent recommendations (8) suggest using both scores in post-stroke recovery assessments. However, many studies and clinical sites still employ only one measure, likely due to logistical constraints and to minimize effort for both patients and personnel (49–51). This makes it challenging to compare results across studies. Our analysis of categorical agreement between FMMA-UE and ARAT scores at the acute/early subacute, subacute, and chronic stages provide the ability to compare data across studies and clinical sites where only one measure may be available.

Interestingly and similar to Hoonhorst et al., we found a decreased specificity between the FMMA-UE cut-off scores and ARAT categories at the higher ranges, specifically in the "notable versus full" categories at the chronic stage. This divergence between scores at high functional levels suggests that, even with a perfect FMMA-UE score, a remaining deficit may prevent reaching full activity potential. This may be best explained by the fact that fine motor skills are underrepresented in the FMMA-UE assessment, despite being important for achieving full ARAT scores (24).

These results do not imply the redundancy of either assessment tool. The FMMA-UE and the ARAT have previously shown to be highly correlated; however, they are designed to measure different concepts: body impairment versus activity limitation. This is supported by studies that have shown dissociations between these measures, with improvements in one measure but not the other [e.g., (52–54)]. As summarized by Demers and colleagues, movement can be classified at two levels: end point movement in external space (measured by variables such as trajectory speed, precision, and straightness) and movement in body space (measured by variables such as joint ranges, interjoint coordination, and muscle activation patterns) (55). Improvements in end point characteristics can occur through either compensation (e.g., trunk movement to assist reaching) or true recovery of movement in body space. Only movement quality variables in body space can distinguish whether recovery or compensation has occurred.

The ARAT includes speed as a core component, an end point characteristic that can be improved by either restoration or compensation. The test deducts points for compensatory movements, meaning an item cannot receive the full score (three points) if compensatory movements are involved. Furthermore, a score of two is given in the presence of slower movements and/or in the presence of compensatory movements. As such, it does not differentiate well between these factors. Lower scores of one or zero points are given if the task is not fully completed. Because of this scoring system, the ARAT can identify some compensatory movements but does not differentiate them from other sources of movement abnormalities. In contrast, the FMMA-UE does not use this scoring system.

We anticipated that FMMA-UE and ARAT scores would initially align closely in the acute/early subacute phase, reflecting restoration-based recovery as the main driver behind both assessments. As recovery progresses beyond the subacute stage, we expected compensatory strategies to create a divergence between ARAT and FMMA-UE scores, with ARAT scoring allowing for further gains due to compensatory strategies for task

completion (55). Thus, we expected decreased sensitivity and specificity of cut-off scores in the chronic phase after the restoration plateau. However, the consistent association between FMMA-UE and ARAT across different recovery stages suggests that these scores alone cannot adequately evaluate differences based on restoration versus compensation (55). Considering this, our findings reinforce recent recommendations advocating for the inclusion of kinematic assessments or explicit evaluations of motor control (5, 55). Such assessments could provide a more nuanced understanding of post-stroke recovery, thereby facilitating tailored rehabilitation strategies.

The primary limitation of this study was its reliance on data from previous studies, which, due to differing time points, were used for cross-sectionally analysis at each specified recovery stage. We compared the ability of FMMA-UE cut-off scores to predict ARAT-based functional categories at different stages of recovery. Additionally, while the established Minimal Clinically Important Difference (MCID) and Minimal Detectable Change (MDC) values provided useful benchmarks, they should be interpreted with caution. We utilized both metrics in our study to ensure a comprehensive analysis, acknowledging that these represent the best available measures under current methodological constraints.

In summary, our study revealed that FMMA-UE can classify upper extremity functional categories as defined by performance on the ARAT across all stages of stroke recovery. This is both scientifically relevant and clinically meaningful because it allows for a more standardized approach to evaluating post-stroke recovery. Additionally, the high congruence of both measures throughout different stages of recovery indicates that they are not suited to comprehensively capture the difference between restitution of impairment versus improvement. These findings emphasize the need to include assessments, such as kinematics, that allow for better measurement of recovery to enhance our understanding of upper limb functionality throughout rehabilitation.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data analyzed in this study was obtained from the University of Zurich and cereneo Center for neurology and rehabilitation, the following licenses/restrictions apply: the dataset analyzed in this study is available upon reasonable request. Requests to access these datasets should be directed to AL, Department of Neurology, University Hospital Zurich, University of Zurich, Zurich, Switzerland, andreas.luft@usz.ch. Requests to access these datasets should be directed to AL, andreas.luft@usz.ch.

Ethics statement

The studies involving humans were approved by the ethics committee of Zurich and the ethics committee of Northwest and Central Switzerland. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BV: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. RK: Investigation, Methodology, Resources, Validation, Writing – review & editing. JP: Data curation, Investigation, Resources, Writing – review & editing. JH: Data curation, Investigation, Resources, Writing – review & editing. AL: Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. JV: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – review & editing. MB: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

Data which were reused from the studies aRISE, reUSE, and ISEAR, were funded by Boehringer Ingelheim.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1429929/full#supplementary-material

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Effects of body weight support training on balance and walking function in stroke patients: a systematic review and meta-analysis

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Objective: To comprehensively and quantitatively evaluate the impact of body weight support training (BWST) on balance and gait function in stroke patients based on an evidence-based basis and to identify the most effective intervention strategies.

Methods: PubMed, Web of Science, The Cochrane Library, CNKI, Wanfang, and Chinese SinoMed Database were searched until November 25, 2023. Quality assessment and meta-analysis were performed using RevMan 5.2 and Stata 14.0 software.

Results: A total of 31 randomized controlled trials involving 1,918 patients were included in the study. The meta-analysis demonstrated that body weight support training (BWST) significantly improved Berg Balance Scale (BBS) scores (MD = 3.60; 95% CI: 1.23 to 5.98; $p = 0.003$), gait speed (SMD = 0.77; 95% CI: 0.38 to 1.15; $p < 0.0001$), and step length (SMD = 0.46; 95% CI: 0.19 to 0.72; $p = 0.0008$) in stroke patients compared to conventional rehabilitation. For enhancing balance function, the most effective interventions were identified as a disease duration of 3–6 months (MD = 5.16; 95% CI: 0.76 to 9.57; $p = 0.02$), intervention time of 4–8 weeks (MD = 5.70; 95% CI: 2.90 to 8.50; $p < 0.0001$), a maximum body weight support level above 30% (MD = 3.80; 95% CI: 1.48 to 6.13; $p = 0.001$), and a maximum training walking speed of 0.2 m/s or more (MD = 4.66; 95% CI: 0.37 to 9.70; $p = 0.03$). For improving walking function, the optimal interventions were also a disease duration of 3–6 months (gait speed: SMD = 0.59; 95% CI: 0.15 to 1.03; $p = 0.008$; step length: SMD = 0.27; 95% CI: 0.06 to 0.56; $p = 0.04$), intervention time of 4–8 weeks (gait speed: SMD = 1.01; 95% CI: 0.44 to 1.59; $p = 0.0006$; step length: SMD = 0.83; 95% CI: 0.54 to 1.12; $p < 0.00001$), a maximum body weight support level above 30% (gait speed: SMD = 0.79; 95% CI: 0.36 to 1.22; $p = 0.0003$; step length: SMD = 0.79; 95% CI: 0.47 to 1.11; $p < 0.00001$), and a maximum training walking speed of 0.2 m/s or more (gait speed: SMD = 1.26; 95% CI: 0.62 to 1.90; $p = 0.0001$; step length: SMD = 0.85; 95% CI: 0.38 to 1.31; $p = 0.0003$).

Conclusion: Compared with conventional rehabilitation training, BWST demonstrates superior efficacy in enhancing balance and walking function in stroke patients, with a consistent optimal intervention strategy. The most effective program includes a disease duration of 3–6 months, an intervention period of 4–8 weeks, a maximum body weight support of 30% or more, and a maximum training walking speed of 0.2 m/s or greater.

Systematic review registration: http://www.crd.york.ac.uk/PROSPERO/, identifier: CRD42022358963.

KEYWORDS

body weight support training, stroke, balance, walking function, meta-analysis

Introduction

Stroke is one of the most prevalent neurological disorders globally. The primary objective of rehabilitation for early-stage stroke patients is to restore lower limb motor function, particularly on balance and walking abilities (1). Previous studies have indicated (1, 2) that over 80% of stroke patients experience balance and walking dysfunction during the acute/subacute phase, characterized by impaired postural alignment, increased sway, asymmetrical gait, and diminished responsiveness to external forces. These impairments significantly reduce patients' independence and quality of life in performing basic activities of daily living and impose a substantial psychological burden (3, 4). Therefore, finding the best and most effective intervention program for restoring motor function in stroke patients is a key goal for patients (5) and remains a critical scientific issue of significant interest in the field of rehabilitation.

Body weight support training (BWST) is an innovative rehabilitation method that utilizes suspension or pneumatic compression techniques to reduce the effective load of the patient's body weight during exercise (6). Stroke patients often suffer from overall neurological and motor decline, so their rehabilitation interventions are more demanding than those for single sports injuries (7, 8). BWST is a crucial intervention to reduce weight load, enabling patients to perform comprehensive gait exercises. This approach is better suited to the holistic rehabilitation required by stroke patients than conventional rehabilitation methods and facilitates motor relearning and neural pathway reorganization (9, 10). BWST has been increasingly employed in stroke rehabilitation in recent years, demonstrating notable efficacy (1). A recent study (11) indicated that BWST could significantly enhance lower limb motor function and rehabilitation outcomes, improve patients' ability to perform daily activities and enhance their quality of life, thereby accelerating their reintegration into family and society. However, previous studies have reported varying results regarding how BWST improves balance and walking function in stroke patients (12, 13). These discrepancies may stem from differences in disease duration and training parameter settings (such as training intensity or intervention time). While earlier research (14–19) has examined individual training parameters (e.g., training time, load), these studies were limited by small sample sizes and the specific characteristics of the included patients, resulting in findings with certain limitations. More importantly, previous intervention trials could only investigate the effect of a single intervention element without exploring the combined effects of different aspects from a multidimensional perspective. Consequently, the optimal intervention program remains undefined.

Therefore, this study aimed to adopt an evidence-based medicine approach to comprehensively and quantitatively assess the effects of BWST on balance and walking function in stroke patients through meta-analysis. Additionally, it sought to identify the optimal intervention program, aiming to discover the most effective rehabilitation strategies for stroke patients and provide valuable references for developing exercise prescriptions.

Methods

This review was registered (Identifier: CRD42022358963) in the International Prospective Register of Systematic Reviews (PROSPERO) and complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (20).

Study search and selection

We conducted a comprehensive literature search across PubMed, Web of Science, The Cochrane Library, CNKI, Wanfang, and Chinese SinoMed Databases until November 2023, without any language restrictions. The search terms included (a) Stroke or Cerebral stroke, Cerebral vascular accident or CVA, and (b) Antigravity treadmill or Body weight support. Taking the PubMed database as an example, the specific search strategy is: ((((Stroke [Title/Abstract]) OR (cerebral stroke [Title/Abstract])) OR (cerebral vascular accident [Title/Abstract])) OR (CVA [Title/Abstract])) AND ((antigravity treadmill [Title/Abstract]) OR (body weight support [Title/Abstract])).

The inclusion criteria for this meta-analysis were: (a) the study was a randomized controlled trial, (b) participants were patients with a clinical diagnosis of stroke, (c) interventions involved BWST combined with conventional rehabilitation treatments for the trial group and conventional rehabilitation treatments only for the control group, and (d) the outcomes included Berg Balance Scale (BBS) scores and walking function parameters such as gait speed and step length. The exclusion criteria were: (a) studies that did not involve BWST interventions, (b) interventions that combined BWST with other therapies, (c) patients with other types of diseases, (d) studies with missing or inconsistent outcomes, (e) conference and dissertation papers, and (f) duplicate publications.

EndNote X9 software was used to remove duplicate records from the search results. The title and abstract of retrieved articles were initially read and screened by two reviewers (Z.J., X.Z.) using an independent double-blind approach following the study inclusion and exclusion criteria. Articles that might meet the inclusion criteria were downloaded in full text and read for re-screening to finalize the article's inclusion. For articles with divergent extractions by two reviewers, a third reviewer (Y.T.) was added to decide on inclusion through joint discussion.

Data extraction and quality assessment

Two reviewers (Z.J. and X.Z.) independently extracted data from the included articles using a pre-designed form. The extracted information primarily included: (1) basic information about the article, such as the first author and year of publication; (2) basic information about the trial participants, including sample size, age,

and disease duration; (3) details of the trial intervention, such as intervention time, frequency, degree of body weight support, and training speed; and (4) baseline and endpoint data of the outcomes.

The risk of bias for the included articles was assessed using the Cochrane Collaboration's risk-of-bias guidelines (21). This evaluation covered seven key areas: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessments, (5) incomplete outcome data, (6) selective reporting, and (7) other biases. Two reviewers (X.Z. and Q.F.) conducted the quality assessment independently. In cases of disagreement, a third reviewer (Y.T.) was involved to reach a consensus through discussion.

Data synthesis and statistical analysis

Forest plots and subgroup analyses were conducted using RevMan 5.2 software, while funnel plots, sensitivity analyses, meta-regression, and publication bias tests (Egger's method) were performed using Stata 14.0 software. Effect sizes were reported as mean ± standard deviation with 95% Confidence Intervals (95% CI). Mean Difference (MD) was used for outcomes measured in the same units, while Standardized Mean Difference (SMD) was used for outcomes in different units (22). The Chi^2 test and I^2 statistic were used to assess study heterogeneity, with analyses conducted using RevMan 5.2 and Stata 14.0 software. A fixed-effects model was applied if heterogeneity was not statistically significant ($I^2 < 50\%$; $p > 0.05$); otherwise, a random-effects model was employed (23). Sensitivity analyses were conducted for outcomes with heterogeneity to evaluate the stability of findings, and meta-regression analyses were used to explore sources of heterogeneity. Based on study characteristics, subgroup analyses assessed moderating variables that might influence effect sizes. Statistical significance was set at $\alpha = 0.05$, with $p < 0.05$ indicating significance.

Results

Search results

A total of 712 records were retrieved. After removing duplicates using EndNote, 556 records remained for initial screening. After reviewing titles and abstracts, 463 articles were excluded for irrelevance. The remaining 93 studies were then re-screened through full-text review, excluding 62 studies that did not meet the inclusion criteria. Ultimately, 31 studies were included in the meta-analysis (1, 11–13, 19, 24–49). The literature screening process is depicted in Figure 1.

Methodological quality assessment

The 31 studies in the meta-analysis involved 1,918 participants, with basic study information detailed in Table 1. The quality of the included studies was assessed using the Cochrane Risk of Bias Assessment Tool. Studies were classified as having a low risk of bias if all seven aspects were evaluated as "low risk." If one or two aspects were rated as "high risk" or "uncertain risk," the study was considered to have a moderate risk of bias. Studies with more than two aspects rated as "high risk" or "uncertain risk" were classified as having a high risk of bias. Based on this, six studies were evaluated as low risk of bias (12, 29, 32, 43, 45, 48), four studies were evaluated as moderate risk of bias (11, 19, 42, 44), and 21 studies were evaluated as high risk of bias (1, 13, 24–28, 30, 31, 33–41, 46, 47, 49). All studies had a low risk of incomplete outcome data and selective reporting and a high risk of random sequence generation. The evaluation results are shown in Figure 2.

Meta-analytic results

Effect of BWST on BBS scores

Twenty-two of the 31 included studies (1, 19, 24–26, 29–35, 37, 38, 40, 42, 44–49) were analyzed for BBS scores. Due to high heterogeneity among the combined results ($I^2 = 98\%$), a random effects model was employed for the meta-analysis. The combined effect size indicated a significant improvement in BBS scores in the BWST group compared to the control group (MD = 3.60; 95% CI: 1.23–5.98; $p = 0.003$). The results are presented in Figure 3.

To investigate the effects of relevant moderating variables on the results of the study, four moderating variables were extracted based on the characteristics of the included studies, namely, patients' disease duration, intervention time, maximum degree of body weight support, and maximum training gait speed. A subgroup analysis based on the above moderating variables found (as shown in Table 2) that the intervention was most effective for patients with a disease duration of 3–6 months (MD = 5.16; 95% CI: 0.76 to 9.57; $p = 0.02$). No statistically significant effects were observed for patients with a disease duration of 1–3 months (MD = 4.78; 95% CI: −1.80 to 11.36; $p = 0.15$) or more than 6 months (MD = 0.04; 95% CI: −0.32 to 0.40; $p = 0.82$). The most effective treatment was observed with an intervention duration of 4–8 weeks (MD = 5.70; 95% CI: 2.90–8.50; $p < 0.0001$). Interventions lasting 1–4 weeks (MD = −0.04; 95% CI: −3.28 to 3.19; $p = 0.98$) or more than 8 weeks (MD = 6.32; 95% CI: −2.61 to 15.26; $p = 0.17$) showed no statistically significant effect. An intervention with a maximum body weight support of 30% or more was effective (MD = 3.80; 95% CI: 1.48–6.13; $p = 0.001$). Support of 0–30% did not show a statistically significant treatment effect (MD = 1.34; 95% CI: −4.04 to 6.73; $p = 0.62$). A maximum training gait speed of 0.2 m/s or more significantly improved balance function (MD = 4.66; 95% CI: 0.37–9.70; $p = 0.03$), while speeds of 0–0.2 m/s did not show a statistically significant effect (MD = 2.96; 95% CI: −0.83 to 6.75; $p = 0.13$). In conclusion, BWST was most effective in improving BBS scores in stroke patients with a disease duration of 3–6 months, an intervention time of 4–8 weeks, a maximum body weight support of 30% or more, and a maximum training gait speed of 0.2 m/s or more.

Additionally, meta-regression analysis was conducted to identify significant factors influencing heterogeneity when the number of studies exceeded ten and the heterogeneity I^2 was >50%. The results (shown in Table 3) indicated that intervention time ($p = 0.319$), maximum body weight support ($p = 0.302$), and maximum training gait speed ($p = 0.441$) did not significantly contribute to heterogeneity. In contrast, disease duration showed a statistically significant result ($p = 0.046$), suggesting it may be the primary source of heterogeneity.

Effect of BWST on walking function

A total of 14 (11–13, 19, 24–28, 36, 41, 43, 44, 49) of the 31 included studies analyzed gait speed. Due to significant heterogeneity among the results ($I^2 = 87\%$), a random effects model was employed

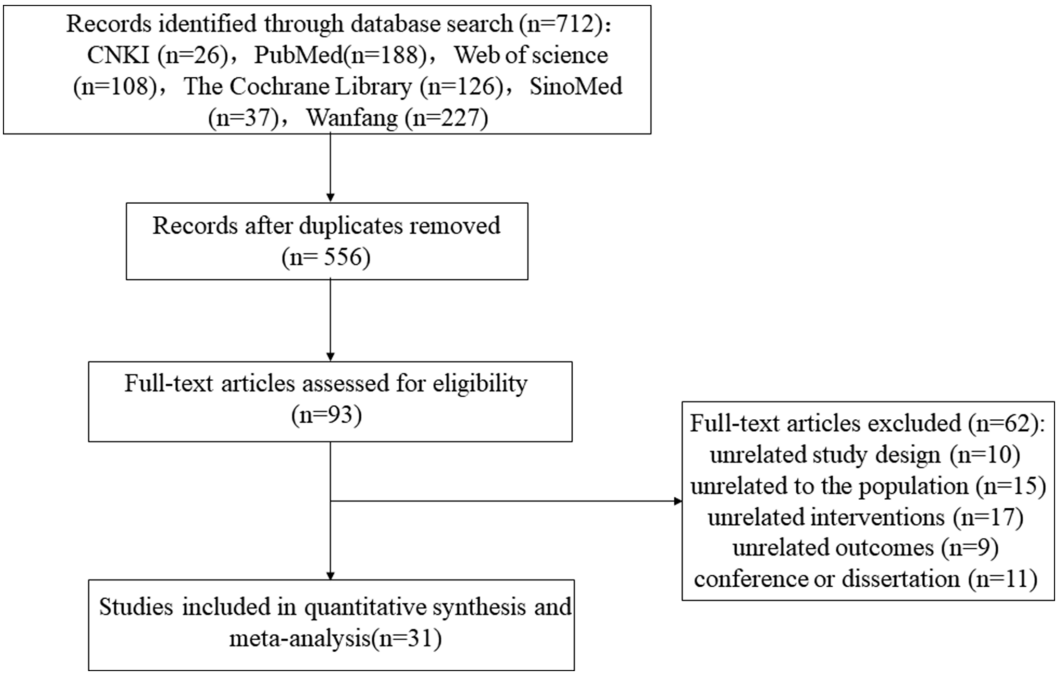

FIGURE 1
The flow diagram of the selection process.

for the meta-analysis. The combined effect size demonstrated a significantly greater gait speed in the BWST group than in the control group (SMD = 0.77; 95% CI: 0.38 to 1.15; $p < 0.0001$, Figure 4). Additionally, 10 (11, 13, 19, 26, 27, 36, 38, 41, 43, 49) of the 31 studies included analyzed step length. Given the large heterogeneity in the combined results ($I^2 = 58\%$), a random effects model was also used for the meta-analysis. The combined effect size revealed a significantly greater improvement in step length for the BWST group compared to the control group (SMD = 0.46; 95% CI: 0.19–0.72; $p = 0.0008$, Figure 5).

Also, subgroup analyses were conducted to explore the impact of relevant moderating variables—disease duration, intervention time, maximum degree of body weight support, and maximum training gait speed—on study outcomes (Table 4). It was found that in terms of the gait speed outcome, the intervention was most effective for patients with a disease duration of 3–6 months (SMD = 0.59; 95% CI: 0.15–1.03; $p = 0.008$). No significant effects were observed for durations of 1–3 months (SMD = 0.57; 95% CI: −0.07 to 1.22; $p = 0.08$) or more than 6 months (SMD = 0.32; 95% CI: −0.31 to 0.96; $p = 0.32$). An intervention time of 4–8 weeks showed superior results (SMD = 1.01; 95% CI: 0.44–1.59; $p = 0.0006$) compared to 1–4 weeks (SMD = 0.53; 95% CI: 0.12–0.93; $p = 0.01$). An intervention duration of more than 8 weeks (SMD = 1.18; 95% CI: −0.01 to 2.37; $p = 0.05$) was not statistically significant. Maximum body weight support of 30% or more was more effective (SMD = 0.79; 95% CI: 0.36–1.22; $p = 0.0003$) than support of 0–30% (SMD = 0.67; 95% CI: 0.29–1.05; $p < 0.00001$). A maximum gait speed of 0.2 m/s or more resulted in better outcomes (SMD = 1.26; 95% CI: 0.62–1.90; $p = 0.0001$) compared to speeds of 0–0.2 m/s (SMD = 0.60; 95% CI: 0.29–0.90; $p < 0.00001$). For the step length outcome, the intervention was most effective for a disease duration of 3–6 months (SMD = 0.27; 95% CI: 0.06–0.56; $p = 0.04$). No significant effects were observed for durations of 1–3 months (SMD = 0.44; 95% CI: −0.33 to 1.21; $p = 0.26$) or more than 6 months (SMD = 0.30; 95% CI: −0.03 to 0.64; $p = 0.08$). The best results were achieved with an intervention time of 4–8 weeks (SMD = 0.83; 95% CI: 0.54–1.12; $p < 0.00001$). Interventions lasting 1–4 weeks (SMD = 0.17; 95% CI: −0.15 to 0.48; $p = 0.29$) or more than 8 weeks (SMD = 0.30; 95% CI: −0.03 to 0.64; $p = 0.08$) showed no statistically significant effects. A maximum body weight support of 30% or more was most effective (SMD = 0.79; 95% CI: 0.47–1.11; $p < 0.00001$). Support of 0–30% (SMD = 0.14; 95% CI: −0.15 to 0.43; $p = 0.35$) was not statistically significant. A maximum gait speed of 0.2 m/s or more yielded the best results (SMD = 0.85; 95% CI: 0.38–1.31; $p = 0.0003$), while speeds of 0–0.2 m/s (SMD = 0.26; 95% CI: −0.02 to 0.54; $p = 0.05$) showed no significant effect. In summary, BWST with a disease duration of 3–6 months, an intervention time of 4–8 weeks, a maximum body weight support of 30% or more, and a maximum training gait speed of 0.2 m/s or more demonstrated the most effective improvement in balance and walking function in stroke patients.

Meta-regression analysis showed (as shown in Table 5) that the test results for heterogeneity of the disease duration, intervention time, maximum body weight support and maximum training gait speed were not statistically different.

Sensitivity analyses

Due to the high degree of heterogeneity between studies, a study-by-study culling approach was adopted to assess the impact of a single study on the overall effect size based on the overall study. The analysis revealed that the exclusion of single studies had minimal impact on

TABLE 1 The detailed characteristics of each included study.

Year	First author	Sample size (M/F)	Age (Mean ± SD)	Disease duration	Intervention time	Intervention frequency	Maximum body weight support	Training gait speed	Outcomes
2006	Zheng	C: 20/10 E: 25/14	51.2	20–130 days	8–16 weeks	10-15 min/times, 1 time/day, 6 days/week	30–60%	0.25 m/s	Gait speed
2018	Zhao	C: 12/6 E: 11/7	C: 63.7 ± 9.6 E: 65.3 ± 8.1	C: 6.31 ± 2.47 months E: 5.92 ± 2.13 months	4 weeks	30 min/times, 2 time/day, 5 days/week	30–40%	0.2–0.4 m/s	BBS Score
2006	Yang	35/23	53.21 ± 9.68	NR	8 weeks	15-30 min/times, 1 time/ day, 5 days/week	30–40%	NR	Gait speed, step length
2004	Zhao	C: 21/9 E: 15/6	C: 55.15 ± 10.71 E: 54.00 ± 10.71	C: 127.58 ± 68.33 days E: 130.25 ± 64.53 days	6 weeks	30 min/times, 1 time/day, 5 days/week	30–40%	0.14 m/s	Gait speed, step length
2009	Yan	C: 17/8 E: 19/6	C: 55.2 ± 10.9 E: 57.6 ± 10.6	C: 78.8 ± 40.3 days E: 80.6 ± 38.5 days	6 weeks	5-20 min/times, 1 time/ day, 6 days/week	40–50%	10 cm/s	BBS Score
2007	Wu	C: 13/7 0% E: 14/6 30% E: 13/7	C: 57.6 ± 10.8 0%E: 57.3 ± 12.5 30%E: 58.2 ± 11.6	C: 113.8 ± 45.0 days 0%E: 110.8 ± 46.5 days 30%E: 116.2 ± 42.3 days	4 weeks	30 min/times, 1 time/ day, 5 days/week	0或30%	0% E:0.1 m/s 30% E:0.15 m/s	BBS Score, Gait speed, step length
2023	Wang	E: 7/21\u00B0C: 16/16	C: 58.63 ± 5.53 E: 58.81 ± 5.39	C: 22.43 ± 3.08 days E: 22.78 ± 3.25 days	2 months	30 min/times, 1 time/day, 5 days/week	NR	0.27 m/s	BBS Score, Gait speed, step length
2014	Tang	C: 20 E: 20	NR	NR	4 weeks	20-30 min/times, 1 time/ day, 5 days/week	30%	0.01 m/s	BBS Score
2011	Su	43/29	62.8 ± 7.3	NR	NR	NR	NR	NR	BBS Score
2021	Ma	C: 37/23 E: 39/21	C: 58.43 ± 2.14 E: 58.40 ± 2.11	C: 19.78 ± 1.63 days E: 19.81 ± 1.65 days	4 weeks	20-30 min/times, 1 time/day	NR	NR	BBS Score
2021	Lu	C: 28/20 E: 30/18	C: 62.89 ± 3.47 E: 63.02 ± 3.51	NR	28 days	20-30 min/times, 3 time/week	NR	NR	BBS Score
2021	Liu	C: 25/15 E: 26/14	C: 52.1 ± 13.4 E: 53.1 ± 12.8	C: 12.7 ± 4.2 days E: 11.2 ± 4.6 days	4 weeks	30 min/times, 1 time/day, 6 days/week	35%	0.15–0.45 m/s	BBS Score
2013	Liu	C: 17/7 E: 18/6	C: 56.08 ± 5.99 E: 55.23 ± 7.06	C: 60.67 ± 5.95 days E: 61.38 ± 7.56 days	12 weeks	15 min/times, 2 time/day, 5 days/week	NR	NR	BBS Score
2020	Liu	C: 25/22 E: 27/20	C: 58.67 ± 4.12 E: 59.02 ± 4.56	C: 3.51 ± 1.52 months E: 3.67 ± 1.42 months	8 weeks	30 min/times, 1 time/day	NR	NR	BBS Score, Gait speed
2008	Lin C	C: 12/8 E: 11/9	C: 65.5 ± 7.3 E: 66.2 ± 2.4	C: 35–60 days E: 32–58 days	8 weeks	5-30 min/times, 2 time/day, 5 days/week	NR	NR	BBS Score
2008	Lin J	C: 16/7 E: 15/8	C: 53.6 ± 10.2 E: 51.3 ± 10.8	C: 28.7 ± 16.7 days E: 30.5 ± 15.3 days	4–6 weeks	10-30 min/times, 1 time/ day, 5 days/week	40%	0.2-2 m/s	BBS Score
2014	Li	C: 56/44 E: 58/42	C: 61.3 ± 8.9 E: 59.4 ± 9.7	C: 18.1 ± 9.0 days E: 16.4 ± 9.3 days	4 weeks	15-20 min/times, 1 time/day, 5 days/week	40%	0.2–0.4 m/s	BBS Score

(Continued)

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TABLE 1 (Continued)

Year	First author	Sample size (M/F)	Age (Mean ± SD)	Disease duration	Intervention time	Intervention frequency	Maximum body weight support	Training gait speed	Outcomes
2009	Huang	C: 20/11 E: 18/14	C: 58.3 ± 13.4 E: 60.5 ± 11.3	C: 16.5 ± 9.7 days E: 15.3 ± 10.4 days	6 weeks	15-20 min/times, 1 time/day	30%	0.5 m/s	BBS Score
2003	Huang	C: 5/7 E: 5/7	C: 58.3 ± 9.65 E: 57.5 ± 10.56	C: 20.58 ± 14.30 days E: 22.08 ± 25.31 days	2 weeks	5-30 min/times, 1 time/day, 5 days/week	30%	0.2 km/h	BBS Score, Gait speed
2022	Huang	C: 28/22 E: 31/19	C: 53.13 ± 8.23 E: 49.27 ± 5.17	C: 2.48 ± 1.68 years E: 2.74 ± 1.52 years	12 weeks	More than 20 min /times, 1 time/day, 5 days/week	30%	0.15 m/s	Gait speed, step length
2012	Hu	C: 21/13 E: 19/12	C: 61.4 ± 8.5 E: 62.8 ± 7.3	NR	8 weeks	15-30 min/times, 1 time/day, 5 days/week	30–40%	NR	step length, Gait speed
2020	Guo	C: 17/13 E: 15/15	C: 58.4 ± 7.5 E: 57.9 ± 6.4	C: 3.95 ± 1.34 months E: 3.76 ± 1.14 months	2 weeks	30 min/times, 1 time/day, 5 days/week	NR	NR	Gait speed, step length
2008	Chao	37/23	66.7 ± 3.8	NR	8 weeks	15-30 min/times, 1 time/day, 5 days/week	30–40%	NR	BBS Score
1998	Visintin	C: 31/19 E: 30/20	C: 66.7 ± 10.1 E: 66.5 ± 12.8	C: 78.4 ± 30.0 days E: 68.1 ± 26.5 days	6 weeks	Less than 20 min /times, 4 time/week	40%	0–0.1 m/h	BBS Score, Gait speed
2016	Srivastava	C: 12/3 E: 12/3	C: 47.93 ± 9.95 E: 44.2 ± 11.7	C: 442.07 ± 295.13 days E: 391.80 ± 431.10 days	4 weeks	20 min/times, 5 time/week	40%	0–0.16 km/h	Gait speed
2018	Mustafaoglu	C: 11/4 E: 11/4	C: 52.6 ± 14.7 E: 53.7 ± 11.6	C: 11 months E: 12 months	6 weeks	45 min/times, 2 time/week	30–40%	1.2–2.6 km/h	BBS Score
2014	Middleton	C: 16/4 E: 14/9	C: 60.70 ± 14.43 E: 61.39 ± 15.69	C: 29.03 ± 23.90 months E: 50.41 ± 56.80 months	10 weeks	NR	8–50%	NR	BBS Score, step length
2015	Mao	C: 2/7 E: 2/8	C: 60.82 ± 10.7 E: 59.55 ± 9.23	C: 47.67 ± 16.78 days E: 49.25 ± 19.51 days	3 weeks	NR	30–40%	0.5–2.5 m/s	Gait speed, step length
2019	Lura	C: 12/8 E: 15/3	C: 60.4 ± 16.1 E: 63.8 ± 10.8	C: 18.1 ± 4.1 days E: 23.5 ± 8.9 days	NR	NR	NR	NR	step length, Gait speed
2023	Duran	C: 13 E: 13	C: 57.9 ± 10.9 E: 54.1 ± 18.9	C: 10.0 ± 5.1 months E: 12.0 ± 4.0 months	4 weeks	12 times/day, 3 days/week	65–100%	0-2 m/h	BBS Score
2007	Dias	C: 14/6 E: 16/4	C: 68.0 ± 10.69 E: 70.35 ± 7.36	C: 48.45 ± 29.51 days E: 47.10 ± 63.83 days	5 weeks	40 min/times, 5 time/week	30%	NR	BBS Score

E, experimental group; C, control group; NR, not reported; BBS Score, Berg Balance Scale Score.

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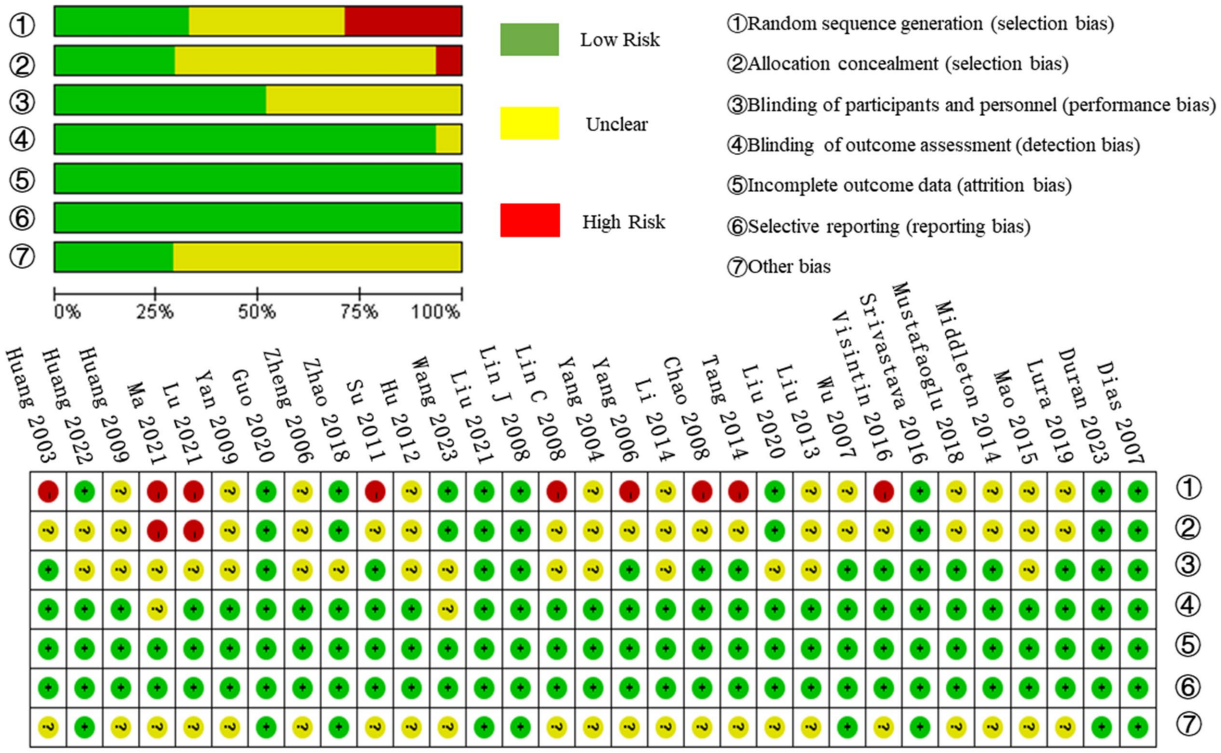

FIGURE 2
Results of quality evaluation of included studies.

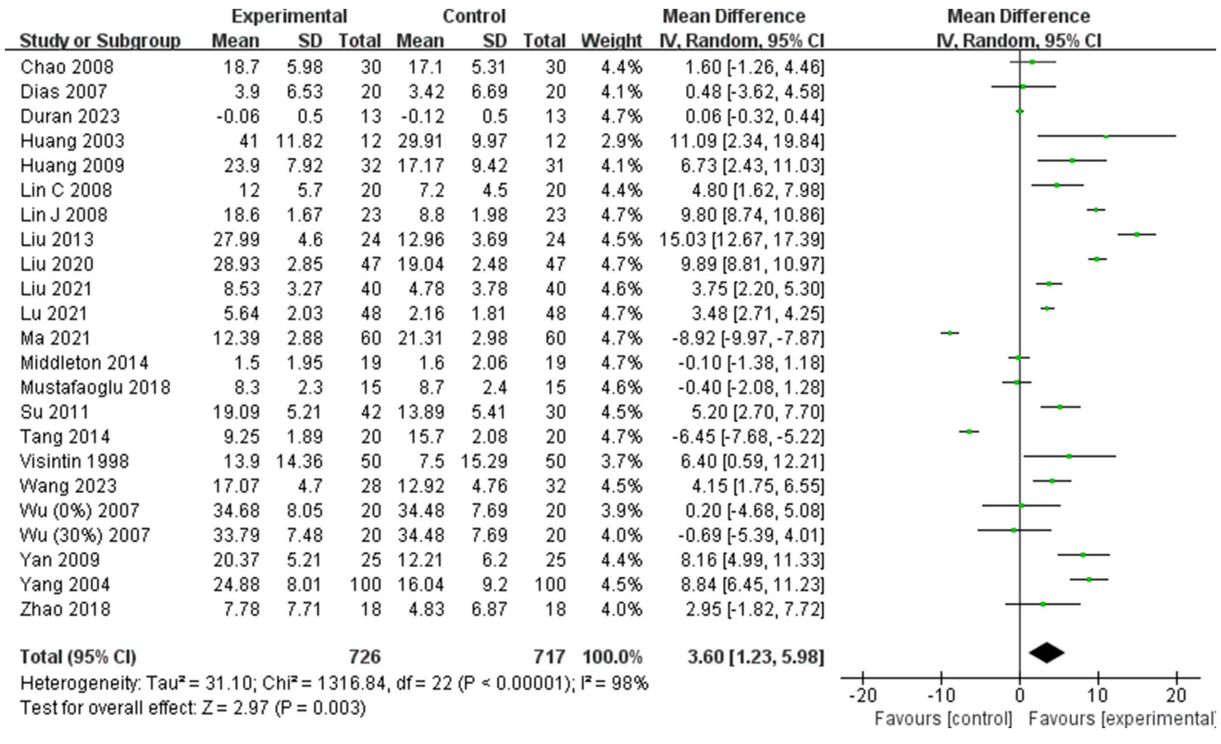

FIGURE 3
Effects of BWST on BBS scores.

TABLE 2 Subgroup analysis of moderating variables affecting BBS scores.

Moderating variables	Subgroup	Sample size	Number of studies	Effect size and 95% CI	I^2 (%)	*p*-value
Disease duration	1–3 months	483	11	4.78 (−1.80, 11.36)	99	0.15
	3–6 months	374	4	5.16 (0.76, 9.57)	90	0.02
	More than 6 months	130	4	0.04 (−0.32, 0.40)	0	0.82
Intervention time	1–4 weeks	502	9	−0.04 (−3.28, 3.19)	98	0.98
	4–8 weeks	723	10	5.70 (2.90, 8.50)	94	<0.0001
	More than 8 weeks	146	3	6.32 (−2.61, 15.26)	98	0.17
Maximum degree of body weight support	0–30%	247	6	1.34 (−4.04, 6.73)	92	0.62
	More than 30%	622	9	3.80 (1.48, 6.13)	92	0.001
Maximum training gait speed	0–0.2 m/s	520	8	2.96 (−0.83, 6.75)	96	0.13
	More than 0.2 m/s	235	5	4.66 (0.37, 9.70)	96	0.03

TABLE 3 Meta-regression analysis of different moderating variables on BBS scores.

Moderating variables	β-regression coefficient	Standard error	*t*-value	P> | *t* |	95%CI
Disease duration	1.600385	0.9079024	1.76	0.046	(0.3151214, 3.515892)
Intervention time	−1.030576	1.009444	−1.02	0.319	(−3.13624, 1.075088)
Maximum degree of body weight support	−1.481964	1.3782	−1.08	0.302	(−4.459383, 1.495456)
Maximum training gait speed	−1.152835	1.44286	−0.8	0.441	(−4.328549, 2.022878)

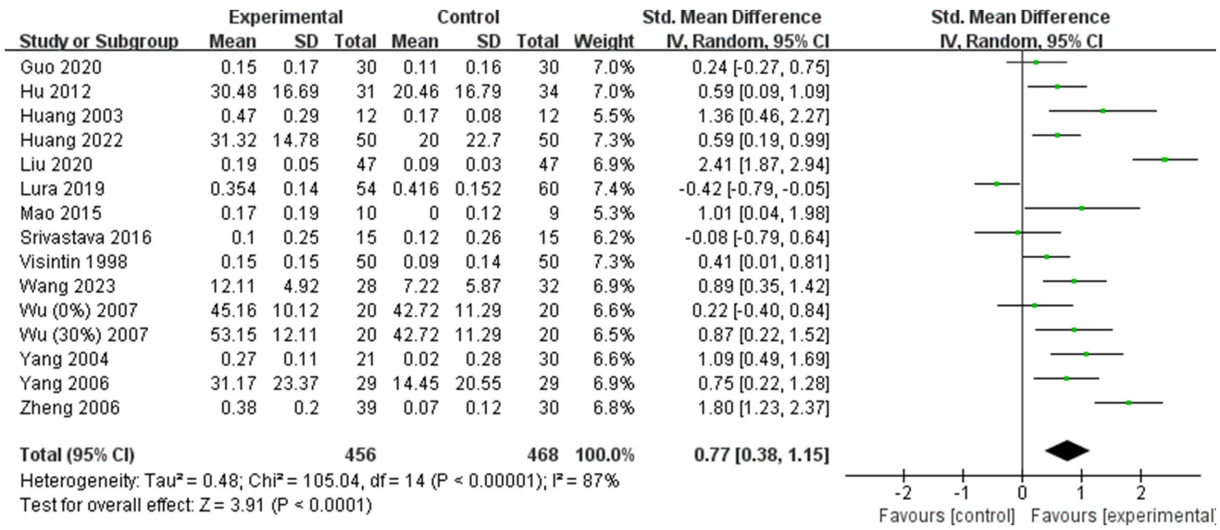

FIGURE 4
Effect of BWST on gait speed.

the overall effect sizes for BBS scores (Figure 6) and gait speed (Figure 7A), indicating the robustness and reliability of the findings for these outcomes.

However, for step length (Figure 7B), the heterogeneity was significantly reduced (I^2 = 42%) following the exclusion of the study by Hu (36). This suggests that Hu's study may have been a significant source of heterogeneity in the step length outcome. Despite this reduction in heterogeneity, the overall effect size for step length remained consistent before and after the exclusion of Hu's study (Post-exclusion: SMD = 0.38; 95% CI: 0.14 to 0.62; p = 0.002). This stability in the effect size confirms that the findings regarding step length are reliable and not unduly influenced by a single study.

Publication bias

The funnel plot and Egger's method were utilized to assess publication bias. The results indicated that BBS scores and walking

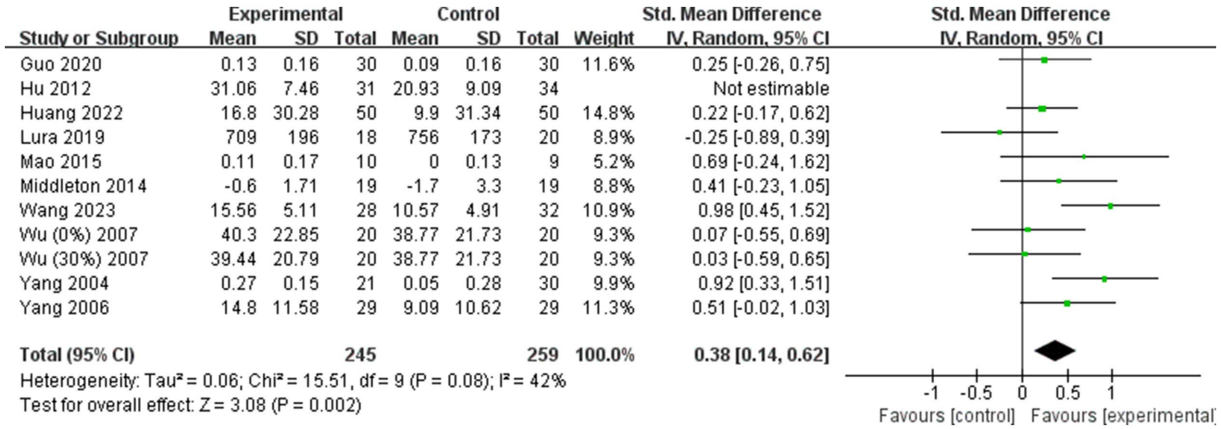

FIGURE 5
Effect of BWST on step length.

TABLE 4 Subgroup analysis of moderating variables affecting walking function.

Outcomes	Moderating variables	Subgroup	Sample size	Number of studies	Effect size and 95% CI	I^2 (%)	P-value
Gait speed	Disease duration	1–3 months	317	5	0.57 (−0.07, 1.22)	85	0.08
		3–6 months	191	4	0.59 (0.15, 1.03)	54	0.008
		More than 6 months	130	2	0.32 (−0.31, 0.96)	60	0.32
	Intervention time	1–4 weeks	213	6	0.53 (0.12, 0.93)	50	0.01
		4–8 weeks	428	6	1.01 (0.44, 1.59)	87	0.0006
		More than 8 weeks	169	2	1.18 (−0.01, 2.37)	91	0.05
	Maximum degree of body weight support	0–30%	204	4	0.67 (0.29, 1.05)	37	<0.00001
		More than 30%	392	7	0.79 (0.36, 1.22)	74	0.0003
	Maximum training gait speed	0–0.2 m/s	385	7	0.60 (0.29, 0.90)	48	<0.00001
		More than 0.2 m/s	148	3	1.26 (0.62, 1.90)	65	0.0001
Step length	Disease duration	1–3 months	117	3	0.44 (−0.33, 1.21)	74	0.26
		3–6 months	191	4	0.27 (0.06, 0.56)	12	0.04
		More than 6 months	138	2	0.30 (−0.03, 0.64)	0	0.08
	Intervention time	1–4 weeks	159	4	0.17 (−0.15, 0.48)	0	0.29
		4–8 weeks	234	4	0.83 (0.54, 1.12)	14	<0.00001
		More than 8 weeks	138	2	0.30 (−0.03, 0.64)	0	0.08
	Maximum degree of body weight support	0–30%	180	3	0.14 (−0.15, 0.43)	0	0.35
		More than 30%	193	4	0.79 (0.47, 1.11)	13	<0.00001
	Maximum training gait speed	0–0.2 m/s	231	4	0.26 (−0.02, 0.54)	11	0.05
		More than 0.2 m/s	79	2	0.85 (0.38, 1.31)	0	0.0003

function outcomes were symmetrically distributed around the funnel plot (Figure 8). Additionally, the Egger's test did not reveal statistically significant differences ($p > 0.05$) (Table 6), suggesting a low probability of publication bias in the study's outcomes.

Discussion

Balance and walking deficits resulting from lower limb motor dysfunction are critical factors influencing stroke patients' ability to return to self-care and reintegrate into family and society (11). The meta-analysis conducted in this study demonstrated that BWST significantly enhances balance and walking function in stroke patients compared to conventional rehabilitation training, aligning with findings from previous research (12, 13).

Several previous studies have confirmed the validity of BBS scores, gait speed and step length as effective measures for evaluating balance and walking function in patients (12, 13). Additionally, the theoretical foundation of BWST in improving motor function is well-established (9, 10), drawing from central pattern generator theory, motor control

TABLE 5 Meta-regression analysis of the effects of different moderating variables on walking function.

Outcomes	Moderating variables	β-regression coefficient	Standard error	*t*-value	P>|*t*|	95%CI
Gait speed	Disease duration	0.6946287	0.4423174	1.57	0.151	(−0.3059628, 1.69522)
	Intervention time	0.2912388	0.4771275	0.61	0.553	(−0.7483327, 1.33081)
	Maximum degree of body weight support	0.6472511	0.6014062	1.08	0.31	(−0.7132243, 2.007727)
	Maximum training gait speed	−0.0573704	0.4608746	−0.12	0.904	(−1.120149, 1.005408)
Step length	Disease duration	0.5537579	0.4223577	1.31	0.231	(−0.4449593, 1.552475)
	Intervention time	0.3312973	0.379584	0.87	0.408	(−0.5440249, 1.20662)
	Maximum degree of body weight support	−0.5708826	0.335209	−1.7	0.149	(−1.432565, 0.2907995)
	Maximum training gait speed	−0.2896365	0.4585486	−0.63	0.562	(−1.562771, 0.9834984)

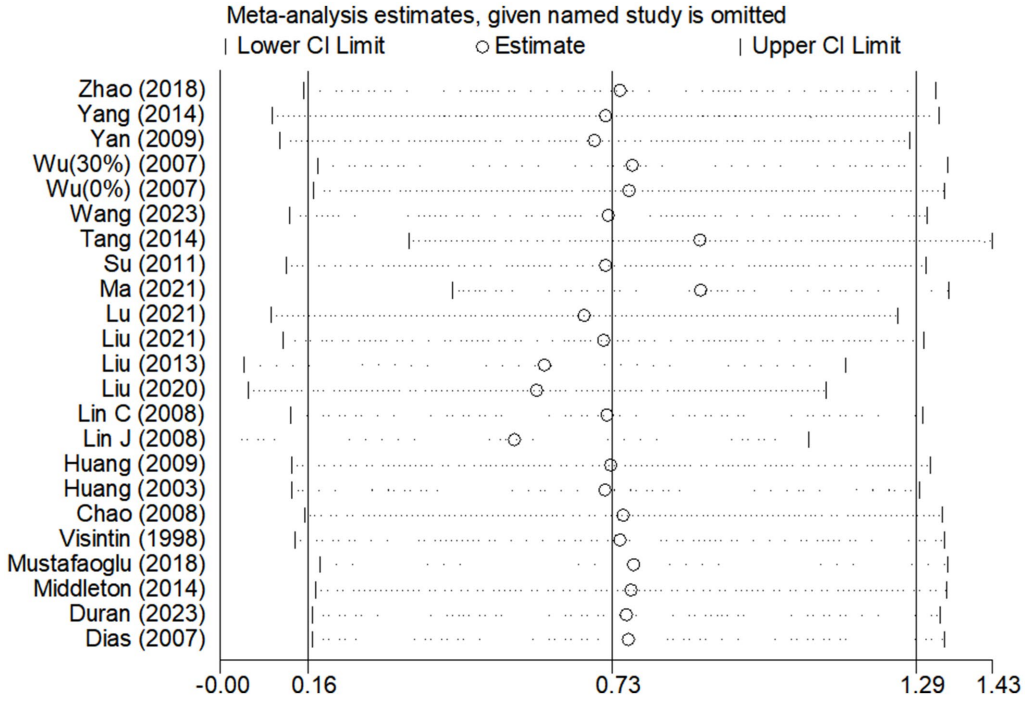

FIGURE 6
Sensitivity analysis of BWST on BBS scores.

dynamical system theory, and the theory of compulsory use (9). The mechanism of BWST involves mandatory exercise with reduced body weight and regulated gait speed, which enhances leg coordination in stroke patients (25) and improves motor relearning and neural pathway reorganization (9, 10).

During training, the therapist can integrate weight bearing, stepping, and balance components by adjusting training loads and body weight support according to the patient's pathology, thereby enhancing proprioceptive input to the lumbar spinal cord and optimizing motor neural pathways, which promotes the consolidation of normal motor patterns (28). Moreover, from a psychological point of view, walking training with adequate safety measures provides patients with a sense of security, reducing anxiety and fear of falling (28). In summary, previous studies have addressed the mechanism of BWST to improve patients' motor function in terms of movement pattern control and development, neural pathway conduction, and psychology. While the mechanisms underlying BWST's effects on motor function are well-explored, there is limited research on the impact of individual differences, training intensity, and duration. Future studies should investigate these aspects further to provide a comprehensive understanding of BWST's therapeutic effects.

The impact of BWST timing parameters on intervention outcomes can be examined through two key dimensions: the initiation and duration of the intervention. This study's subgroup analysis revealed that the intervention time of 4–8 weeks was the best intervention program to improve stroke patients' balance and walking function during 3–6 months of the patient's disease duration. Hayes et al. (50) noted that early rehabilitation training can facilitate faster recovery of lower limb function in post-stroke patients, promoting brain cell regeneration around lesions and enhancing motor function compensation and reorganization in the contralateral cerebral hemisphere (51). However, the specific timing of BWST relative to

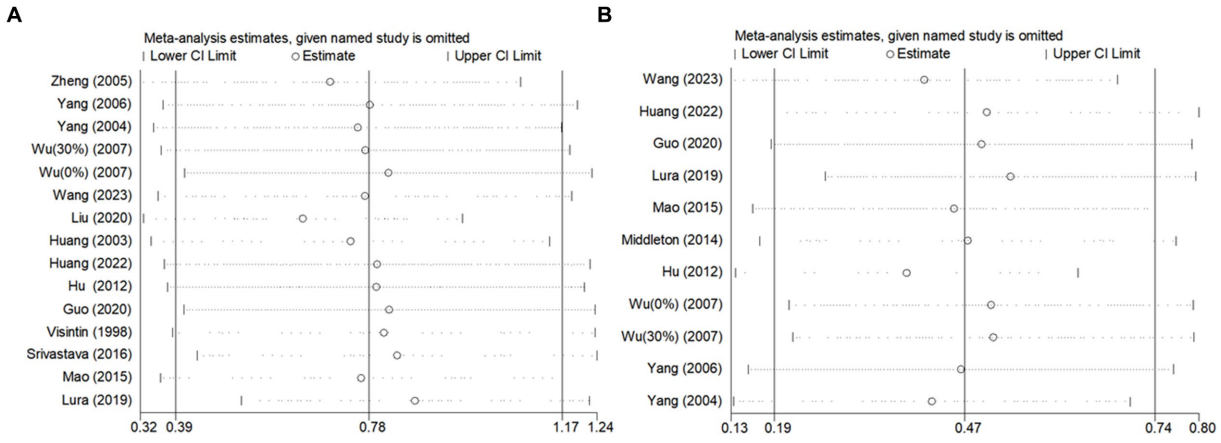

FIGURE 7
Sensitivity analysis of the effect of BWST on walking function (**A**: gait speed, **B**: step length).

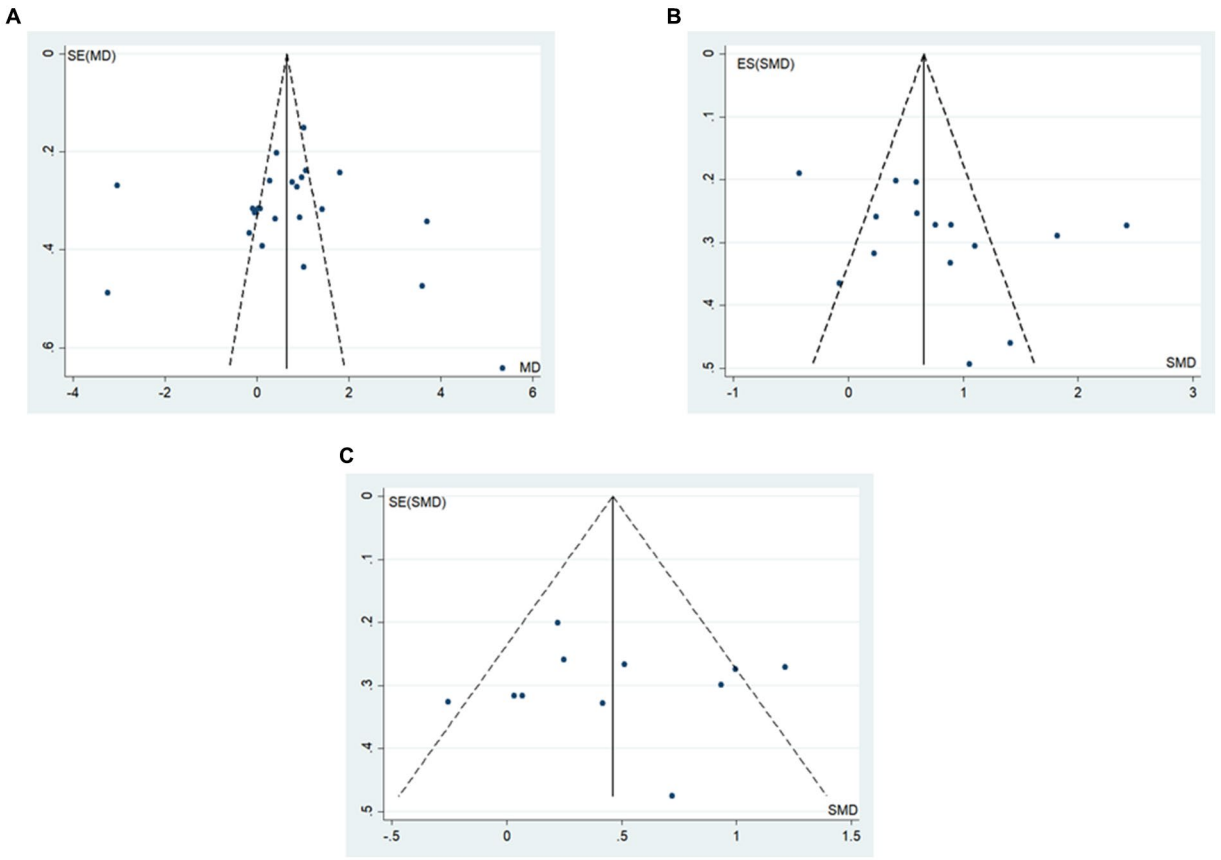

FIGURE 8
Meta-analysis publication bias funnel plot (**A**: BBS score, **B**: gait speed, **C**: step length).

routine rehabilitation is unclear. Song et al. (52) found that BWST is appropriate for patients with stable conditions and lower limb muscle strength of grade 3 or higher. Tong et al. (18) underscored the efficacy of early BWST intervention for recovering lower limb walking function in stroke patients, particularly within the first month of disease duration. Nevertheless, their study focused on patients with a disease duration of less than two months, limiting insights into longer durations. In addition, different intervention times also have a greater impact on the treatment effects of patients, but there are few comparisons of treatment effects based on different intervention cycles. This study demonstrates that for stroke patients with a disease duration of 3–6 months, an intervention period of 4–8 weeks yields the

TABLE 6 Egger's method test results.

Outcomes	Std_Eff	Coef.	Standard error	*t*-value	P> | *t* |	95%CI
BBS scores	Slope	0.4791136	0.9686618	0.49	0.626	(−1.535329, 2.493556)
	Bias	0.6317084	3.388125	0.19	0.854	(−6.414283, 7.6777)
Gait speed	Slope	−0.4889524	0.7478258	−0.65	0.525	(−2.104532, 1.126627)
	Bias	4.369748	2.764352	1.58	0.138	(−1.602271, 10.34177)
Step length	Slope	0.3983997	0.7386791	0.54	0.603	(−1.272608, 2.069408)
	Bias	0.2267712	2.586182	0.09	0.932	(−5.62358, 6.077122)

most favorable outcomes. Further research should explore these findings by including diverse patient populations and controlling intervention timing through randomized controlled trials.

The impact of training load parameters on intervention outcomes is evident in two primary areas: the degree of body weight support and the training gait speed. Previous studies have yielded varying results regarding the optimal degree of body weight support. Liu et al. (15) found that exceeding 50% of the maximum body weight support could induce gait abnormalities, hindering motor function recovery. Conversely, Hesse et al. (53) recommended that body weight support should not surpass 30%. However, the present study's subgroup analysis demonstrated that a maximum body weight support exceeding 30% was more effective for rehabilitation, which diverges from earlier findings. This discrepancy may be attributed to differences in patient characteristics, as previous studies (15, 53) had small sample sizes and patients with a disease duration of approximately 40 days, potentially limiting their conclusions. Expanding patient characteristics and sample size in this study may account for the differing results, warranting further investigation.

Regarding setting the maximum training gait speed, Van et al. (54) argued against using lower speeds for gait training, as it might diminish muscle activation and cause abnormal gait patterns. Wu Hua et al. (16) found that a maximum gait training speed of 0.3 m/s yielded the most significant motor feedback improvement in stroke patients, whereas higher speeds (0.45 m/s) did not enhance motor function. The current study indicates that a maximum training gait speed of 0.2 m/s or more provides the most effective therapeutic outcomes for balance and walking function in stroke patients, suggesting that lower speeds are less effective, though the impact of higher speeds remains unclear. Proper adjustment of training loads according to patient mobility is crucial (55). For less mobile patients, increased body weight support or lower gait speeds may facilitate recovery, while more mobile patients might benefit less. This study's subgroup analyses did not account for variations in patient mobility, and the limitations of included studies restricted further refinement of body weight support and gait speed classifications. Future research should explore the effects of varying body weight support ratios and gait speeds on recovery outcomes by integrating patient characteristics and training loads.

Despite the comprehensive analysis and assessment of all eligible studies, this review has several limitations. Firstly, many of the included studies were of low quality and had a certain risk of bias, which may affect the reliability of the study conclusions. Secondly, literature was excluded due to the absence of relevant outcomes, suggesting that the range of outcomes could be expanded in future research. Thirdly, some subgroups in the analyses were based on a limited number of studies, and the objectivity of these conclusions needs further validation. Future research should focus on randomized controlled trials with larger sample sizes to enhance the robustness of the findings. Additionally, further discussions should explore the impact of variations in patient characteristics and interventions to validate the conclusions of this study.

Conclusion

Compared to conventional rehabilitation, BWST demonstrated superior effectiveness in enhancing balance and walking function in stroke patients. The optimal intervention protocol identified was a 4–8 week treatment time, with a maximum body weight support of 30% or more, and a maximum training gait speed of 0.2 m/s or higher, applied during a 3–6 months disease duration.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

ZJ: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. XZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Writing – original draft. QF: Data curation, Methodology, Writing – original draft. YT: Conceptualization, Data curation, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Global research trends in transcranial magnetic stimulation for stroke (1994–2023): promising, yet requiring further practice

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Background: Scholars have been committed to investigating stroke rehabilitation strategies over many years. Since its invention, transcranial magnetic stimulation (TMS) has been increasingly employed in contemporary stroke rehabilitation research. Evidence has shown the significant potential of TMS in stroke research and treatment.

Objective: This article reviews the research conducted on the use of TMS in stroke from 1994 to 2023. This study applied bibliometric analysis to delineate the current research landscape and to anticipate future research hotspots.

Method: The study utilized the Web of Science Core Collection to retrieve and acquire literature data. Various software tools, including VOSviewer (version 1.6.19), CiteSpace (version 6.3.R1), Scimago Graphica (version 1.0.36), and WPS (version 11572), were used for data analysis and visualization. The review included analyses of countries, institutions, authors, journals, articles, and keywords.

Results: A total of 3,425 articles were collected. The top three countries in terms of publication output were the United States (953 articles), China (546 articles), and Germany (424 articles). The United States also had the highest citation counts (56,764 citations), followed by Germany (35,211 citations) and the United Kingdom (32,383 citations). The top three institutions based on the number of publications were Harvard University with 138 articles, the University of Auckland with 81 articles, and University College London with 80 articles. The most prolific authors were Abo, Masahiro with 54 articles, Fregni, Felipe with 53 articles, and Pascual-Leone, Alvaro with 50 articles. The top three journals in terms of article count were *Neurorehabilitation and Neural Repair* with 139 articles, Clinical *Neurophysiology* with 128 articles, and *Frontiers in Neurology* with 110 articles. The most frequently occurring keywords were stroke (1,275 occurrences), transcranial magnetic stimulation (1,119 occurrences), and rehabilitation (420 occurrences).

Conclusion: The application of TMS in stroke research is rapidly gaining momentum, with the USA leading in publications. Prominent institutions, such as Harvard University and University College London, show potential for collaborative research. The key areas of focus include post-stroke cognitive impairment, aphasia, and dysphagia, which are expected to remain significant

hotspots in future research. Future research should involve large-scale, randomized, and controlled trials in these fields. Additionally, identifying more effective combined therapies with rTMS should be a priority.

KEYWORDS

bibliometric analysis, transcranial magnetic stimulation, stroke, dysphagia, cognitive impairment, research trends, hotspots

1 Introduction

Stroke, a devastating medical condition, has a profound impact on human wellbeing. According to Gorelick, stroke had the highest prevalence in Asia, followed by Eastern Europe and Central Latin America (1). In the United States, ~800,000 individuals are affected by stroke annually (2). The average lifetime cost for each stroke patient was reported to be $140,048 as of 2014 (3). In China, there were 3.94 million new stroke cases, 28.76 million prevalent cases, and 2.19 million deaths attributed to stroke in 2019 (4). An analysis of economic burden revealed that ~3–4% of healthcare expenditure in Western nations is allocated to stroke care (5). Moreover, stroke is a leading cause of long-term disability in the United States, affecting 26% of newly diagnosed patients (6).

Consequently, significant efforts have been directed toward developing rehabilitation and research strategies aimed at addressing the multifaceted challenges of disability, dysfunction, and the economic burden associated with stroke. The diverse range of dysfunction resulting from stroke necessitates a variety of rehabilitation and treatment approaches, with transcranial magnetic stimulation (TMS) emerging as one of the promising methods in this field.

In 1985, Barker et al. pioneered the use of TMS on cortical areas, successfully inducing movement in the contralateral hand or foot, marking the advent of TMS technology (7). Initially, TMS technology was employed as a novel tool for investigating brain function, and it was primarily used to probe the physiological mechanisms underlying stroke and other neurological conditions (8). Subsequently, repetitive transcranial magnetic stimulation (rTMS), a specific mode of TMS, gained prominence in stroke rehabilitation research due to its ability to modify and regulate cortical activity beyond the stimulation period, showing potential as a treatment for neurological disorders. In current times, rTMS is recognized as one of the key rehabilitation modalities for stroke (9). Furthermore, recent years have witnessed an increase in studies focusing on rTMS in the context of stroke rehabilitation (10, 11).

Understanding the key areas of focus and developmental trends in TMS for stroke rehabilitation poses a challenge for new researchers. Therefore, it is essential to actively identify emerging research trends and key areas of interest in this field.

Bibliometrics aims to assist new researchers in comprehending research trends and current hotspots through quantitative and qualitative analysis of literature data. By employing data visualization techniques, bibliometrics allows for a comprehensive analysis of the literature within a database, facilitating comparisons of research focus and collaboration across various countries, institutions, and authors (12). Thus, this review aims to enhance the understanding of evolving trends and significant research hotspots in TMS for stroke, particularly for new researchers.

2 Materials and methods

2.1 Eligibility criteria

This systematic review was conducted in accordance with the PRIBA guidelines (13), ensuring methodological rigor and transparency.

Population: Individuals globally affected by stroke.

Intervention: Transcranial magnetic stimulation (TMS).

Comparators: Various aspects, including the analysis of articles, institutions, citations, author contributions, journals, and keywords.

Outcomes: Detailed outcomes are presented in the subsequent sections on Results and Discussion.

Study design: A range of trials and review articles were included, with a focus on those categorized as "article" or "review article."

2.2 Database

We selected the Clarivate Analytics Web of Science Core Collection (WoSCC), version 2024, as the primary source for our database queries. This database offers extensive citation coverage across a diverse array of core journals, encompassing global research fields such as natural sciences, engineering technology, and biomedicine. It provides comprehensive literature coverage.

2.3 Searching strategy

Initially, we accessed the Web of Science (WoS) platform and navigated to the "WoS Core Collection" and the "Science Citation Index Expanded," covering the period from 1994 to the present. Subsequently, we selected "article" and "review article" as the document types after entering the search query using the following searching subject terms: topic = ("stroke" OR "cerebrovascular accident" OR "hemiparesis" AND "transcranial magnetic stimulation" OR "TMS" OR "rTMS") (14, 15). We excluded the literature published in 2024 and 2025, including non-English literature. Finally, we downloaded the citation report and literature data on the same day, with the research deadline set to 16 March 2024, to ensure consistency and prevent any changes due to data updates.

2.4 Data analysis

First, we selected two researchers to download the data following the same search query mentioned above. The data were not confirmed until two researchers had agreed on the same number of articles to include and to exclude. Second, we used WPS software (version 11572) to analyze the statistical data of top-cited or productive authors, countries, publications, journals, and institutions. Third, we conducted a unified merger for different names of the same country or institution to ensure the accuracy and repeatability of the data. For example, America and the United States of America were merged as the USA. We merged different expressions of the same term for uniformity, such as transcranial magnetic stimulation was merged as TMS. The criteria were saved as a txt document named "same meaning words" and applied in VOSviewer software.

2.5 Data visualization

VOSviewer, a prevalent tool in bibliometric analysis, was employed to visualize the data. It encompassed co-authorship analysis, co-occurrence analysis, citation, and co-citation analysis. Co-authorship analysis examined the number of jointly completed articles to analyze relationships between authors, countries, or institutions. Co-occurrence analysis quantitatively assessed relationships between different projects based on their occurrence together. Co-citation analysis assessed the degree of interconnection between cited works by quantifying the frequency with which they are cited together.

We used VOSviewer software (version 6.19) to visually analyze the literature. The software applied preset values as thresholds during the analysis. Subsequently, the software independently selected and retained the analysis results after removing information with a very low degree of association. We employed CiteSpace (version 6.3.R1) to analyze institutions, authors, co-cited authors, and VOSviewer. We also employed the software Scimago Graphica (version 1.0.36). It was used to examine the collaboration among countries and visualize the global distribution of the world map.

2.6 Research ethics

Ethical approval was not sought as the data for this review was obtained from a publicly accessible database, aligning with ethical guidelines for secondary data analysis.

2.7 The utilization of AI

We have employed Kimi AI (Version: moonshot-v1-20240416), which is a large language model. The application of this process was limited to the entire body of the article, excluding the reference section, for checking mistakes and refining the intended meaning accurately. The refinement procedure was conducted in a collaborative manner, alternating between the AI and the authors, to ensure the accuracy and integrity of the content.

3 Result

3.1 Global trend of publications and citations

By 16 March 2024, our search yielded a comprehensive collection of 3,425 relevant articles. Figure 1 illustrates the study inclusion and exclusion criteria. Figure 2 presents the temporal distribution of publications from 1994 to 2023. Notably, the number of publications related to TMS in stroke generally showed an upward trajectory despite small declines in publication numbers during the years 2008–2009, 2017–2018, and 2022–2023. As of the retrieval date, these articles had accumulated a total of 155,407 citations, averaging 45.37 citations per paper, with an H-index of 171, indicating a significant impact in the field.

3.2 Analysis of top productive countries

Publications in the field of TMS in stroke were contributed by a total of 75 countries. A total of 43 countries met the threshold, as shown in Figure 3, when the threshold was set at five articles for each country. The United Kingdom and Germany were pioneers in TMS research for stroke, with a notable surge in publications in 2012. Italy and the USA experienced a burst of literature around 2014–2016. China experienced a burst of literature around 2020. The USA ranked first with 56,764 citations, followed by Germany with 35,211 citations, and the UK with 32,383 citations, as shown in Table 1. The USA ranked first with 953 articles in terms of publication, followed by China with 546 articles, and Germany with 424 articles, which are among the top three productive countries, as shown in Table 1. Studies of TMS in the field of stroke were more focused on Europe. In the Americas, it was mainly distributed in the USA, Canada, Mexico, Brazil, Chile, and other countries. In Asia, it was mainly distributed in Russia, China, South Korea, and Japan. Oceania was mainly represented by Australia and New Zealand, and Africa was mainly represented by the Republic of South Africa, as shown in Figure 4.

For Figure 3, the size of the circle reflects the number of publications. The connection between the circles reflects the number of citations. The thicker the connection, the more citations it receives, and the color of the circles focuses on different countries according to the scale in the right corner.

3.3 Contributions of top institutions

Among the 3,127 institutions, 424 institutions met the threshold of at least five publications. Table 2 demonstrates that the USA held four out of the top 10 positions. The top three institutions for the number of publications were Harvard University (138 articles), the University of Auckland (81 articles), and University College London (80 articles). The top three institutions in citation ranking were Harvard University (12,813), the National Institute of Neurological Disorders and Stroke (NINDS) (9,621), and University College London (7,506).

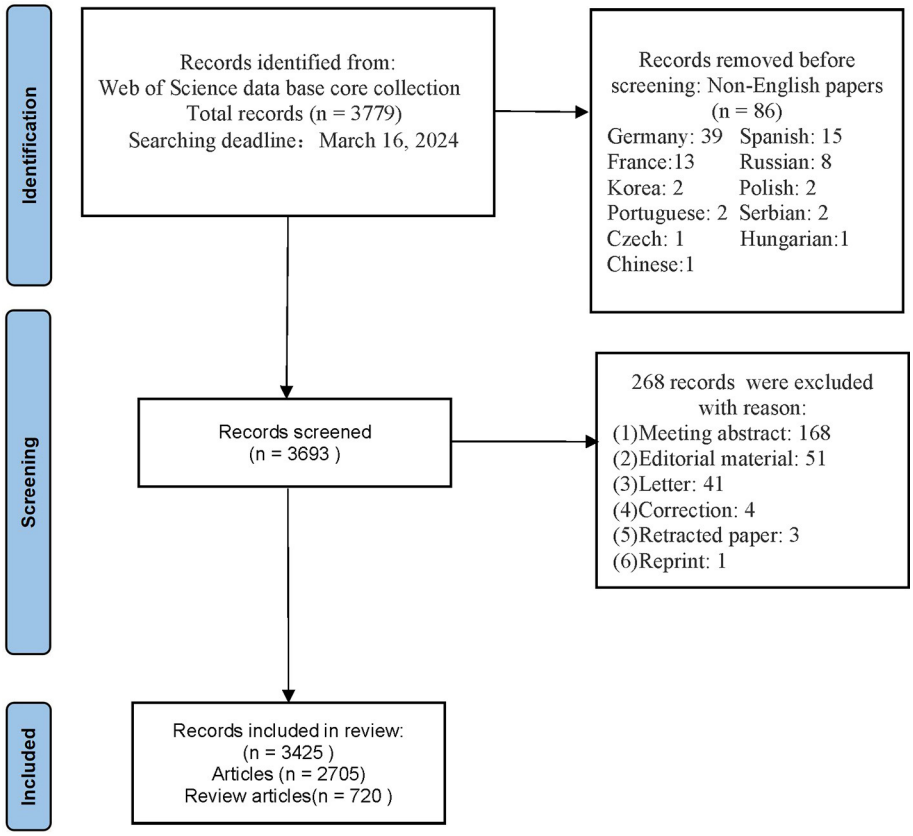

FIGURE 1
Flow chart of literature inclusion and exclusion.

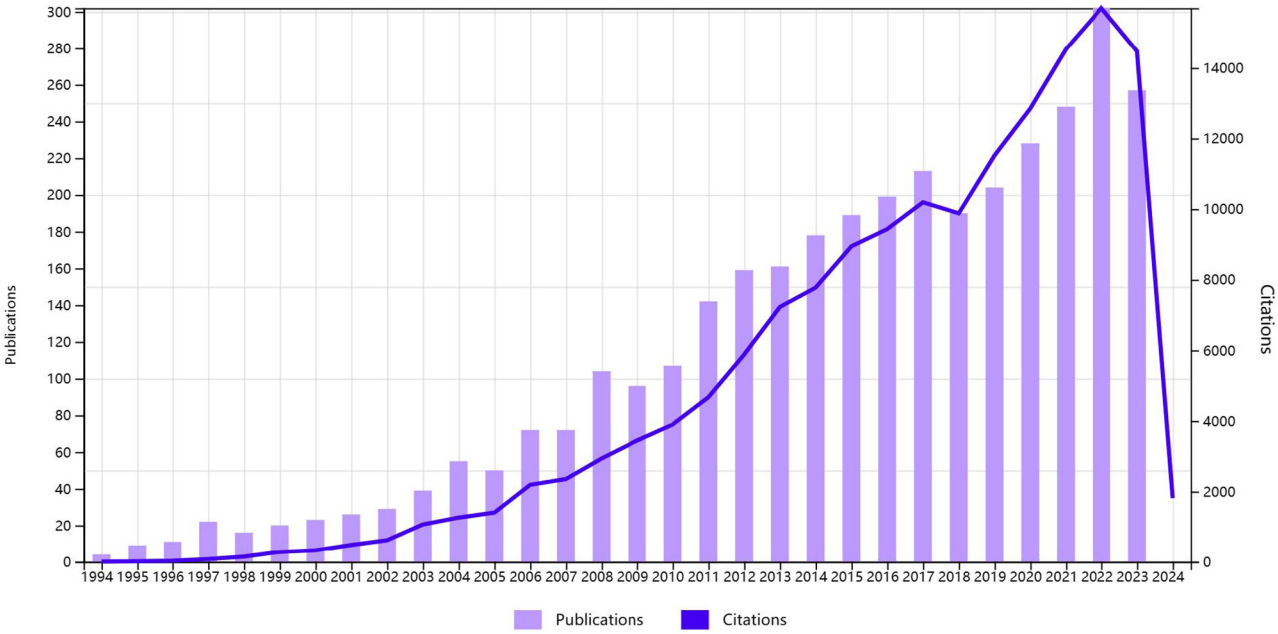

FIGURE 2
Global trend of publications and total citations on TMS research in stroke from 1994 to 2023.

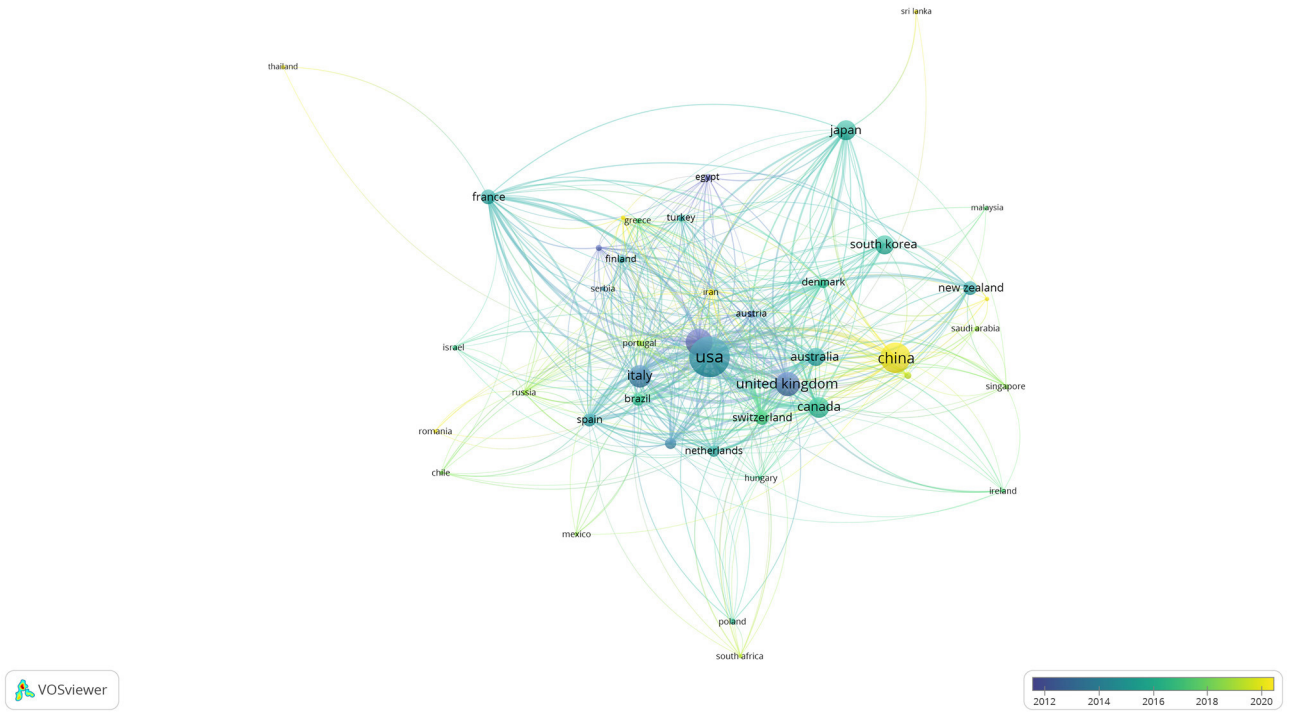

FIGURE 3
Overlay visualization of countries' literature burst.

TABLE 1 The top 10 productive countries/regions related to TMS in stroke.

Rank	Country	Counts	Total citations	Average citation/article	Total link strength
1	USA	953	56,764	59.56	695
2	China	546	7,767	14.23	139
3	Germany	424	35,211	83.04	450
4	United Kingdom	343	32,383	94.41	405
5	Italy	306	22,344	73.02	370
6	Canada	254	11,068	43.57	274
7	Japan	242	9,906	40.93	145
8	South Korea	211	4,627	21.93	61
9	Australia	203	11,123	54.79	283
10	France	131	8,863	67.66	215

Figure 5 shows that 424 institutions have published more than five articles. It also indicated the years during which there was a significant increase in publications from these institutions. The USA experienced a notable surge in literature in 2014, while the National Institute of Neurological Disorders and Stroke (NINDS) saw a similar burst in 2010. Both Harvard University and University College London demonstrated significant betweenness centralities (equal to or >0.1) in the centrality analysis presented in Figure 6. University College London exhibited the highest betweenness centrality at 0.18, highlighting its pivotal role in the research network.

3.4 Analysis of authors and co-cited authors

The analysis comprised a total of 12,306 authors. A total of 491 authors surpassed the threshold of having published at least five articles, highlighting their substantial contributions. The top three authors with the most publications were Abo, Masahiro (54 articles), Fregni, Felipe (53 articles), and Pascual-Leone, Alvaro (50 articles), as indicated in Table 3. The top three authors in terms of citation count were Pascual-Leone, Alvaro (5,361 citations), Fregni, Felipe (4,973 citations), and Cohen, Leonardo G. (4,425 citations).

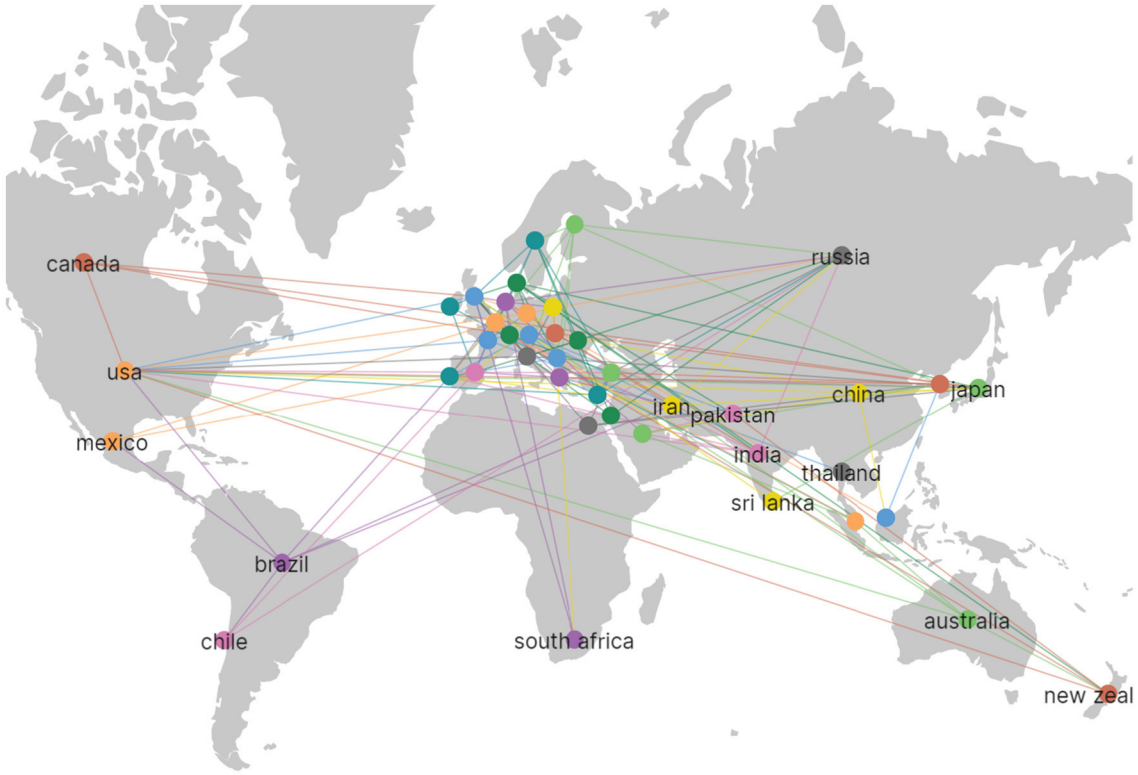

FIGURE 4
It is the distribution map of the countries. The line between countries represents the cooperation among countries.

TABLE 2 The top 10 institutes in the publications concerning the research of TMS in stroke.

Rank	Institution	Country	Counts	Total citations	Total link strength (TLS)	Centrality
1	Harvard University	USA	138	12,813	321	0.13
2	University Auckland	New Zealand	81	4,860	103	0.05
3	University College London	UK	80	7,506	134	0.18
4	National Institute of Neurological Disorders and Stroke (NINDS)	USA	65	9,621	155	0.09
5	Yeungnam University	Korea	62	1,201	17	0.00
6	Emory University	USA	61	2,305	122	0.07
7	University Tubingen	Germany	60	6,910	95	0.07
8	JiKei University	Japan	59	1,176	46	0.02
9	Northwestern University	USA	58	2,131	113	0.03
10	University Manchester	UK	58	4,159	57	0.01

Nitsche, Ma was co-cited 1,258 times. Liepert, J was co-cited 1,123 times, and Rossini, PM was co-cited 1,049 times among the co-cited authors. Rossini, PM, and Khedr, EM had centrality values of 0.10 when the G-index was set at 5, as shown in Figure 7. It indicated their strong recognition of literature in terms of co-citation. The S value was 0.7939, and the Q value was 0.4105, suggesting a good clustering effect and network homogeneity. This showed that the network was well-connected. However, the density value was 0.0606. No individual reached the betweenness centrality in terms of author centrality. The low betweenness centrality values indicated a need to strengthen cooperation between authors.

3.5 Contributions of top journals

Table 4 highlights the top three journals by publication volume: *Neurorehabilitation and Neural Repair* (139 articles), *Clinical Neurophysiology* (128 articles), and *Frontiers in Neurology* (110 articles). The top three journals with the most citations

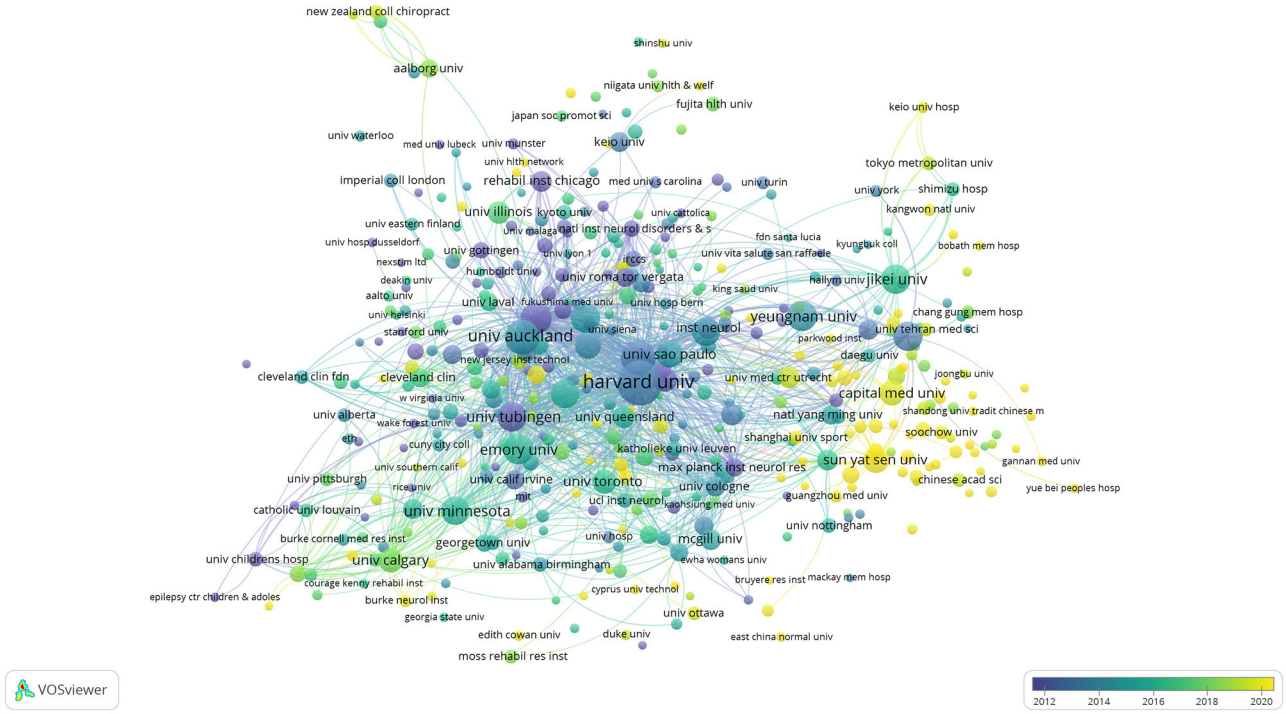

FIGURE 5
The annual distribution of the publishing institutions is visualized using VOSviewer.

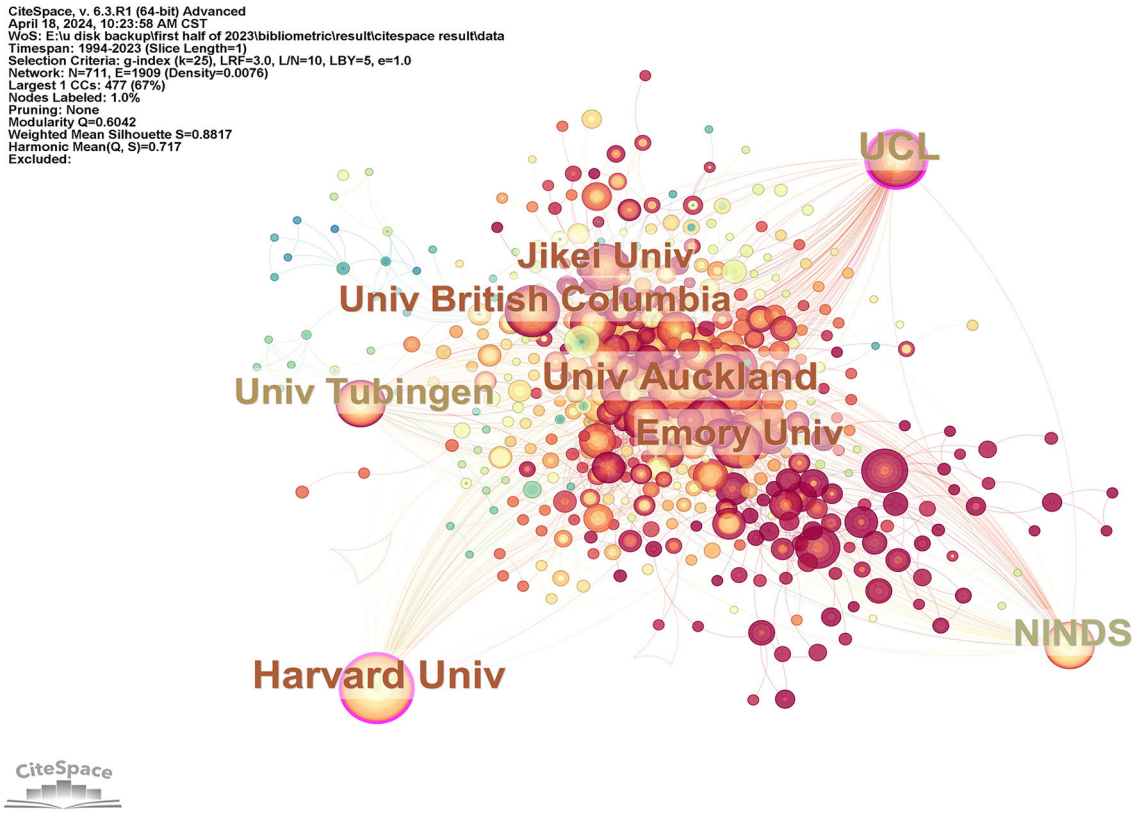

FIGURE 6
It is an institution visualization generated by CiteSpace, and purple circles in the visualization indicate that the centrality of institutions is >0.1.

were *Clinical Neurophysiology* (10,544 citations), *Brain* (10,128 citations), and *Stroke* (9,724 citations).

3.6 Analysis of top cited references and co-citation references

In Supplementary Tables 1, 2, a total of 1,618 references met the threshold of 20 citations. The top three articles in terms of citations were those of Langhorne, P. et al. (1,578 citations), Winstein, C. J. et al. (1,555 citations), and Lefaucheur, J. P. et al. (1,289 citations). The total number of co-citations reached 80,636. A total number of 1,361 references reached the threshold of 20 co-citations. The top 3 references in terms of co-citation were Murase, N. et al. (499 co-citations), Rossi, S. et al. (448 co-citations), and Rossini, P. M. et al. (371 co-citations). The top three in terms of total link strength were Murase, N. et al. (15,764), Takeuchi, N. et al. (9,710), and Hummel, F. et al. (9,279).

3.7 Co-occurrence analysis of keywords

The co-occurrence analysis included 4,355 "author keywords" with 397 keywords meeting the threshold of at least five occurrences. Table 5 presents the top three keywords with the highest frequency: "stroke" (1,275 times), "transcranial magnetic stimulation" (1,119 times), and "rehabilitation" (420 times). Figure 8 illustrates the overlay visualization of keywords. It showed that studies on "cortical stimulation," "intracortical inhibition," and "magnetic stimulation" were focused around the year 2012. Research focus shifted to "transcranial magnetic stimulation" and "functional magnetic resonance" from 2012 to 2016. The focus turned to "stroke" and "aphasia" during the period around 2016 subsequently. The research focused on "repetitive transcranial magnetic stimulation," "dysphagia," and "non-invasive brain stimulation" around 2018. The latest research focused on "high-frequency repetitive trans" and "cognitive function" around 2020.

4 Discussion

The discussion was organized into two main sections and was structured as follows. The first section involved a review of TMS applications in stroke (4.1), where we explored the use of TMS for addressing various post-stroke dysfunctions, such as motor impairments, aphasia, dysphagia, and cognitive impairment. The second part presented the bibliometric analysis of TMS in stroke research (4.2), where various aspects, such as the involvement of countries, institutions, authors, journals, and keywords were examined. Analysis revealed several research hotspots. Based on a thorough analysis of both sections, the conclusion was formulated.

4.1 A review of rTMS in the application of stroke

TMS is a good option for non-invasive brain stimulation, but when it comes to stroke rehabilitation, rTMS, which is a more advanced mode of TMS developed 4–8 years after the initial development of TMS, is often used as therapy. rTMS has controllable and repetitive frequency capabilities. It can be divided into high frequency (HF≥1 Hz; HF-rTMS) and low frequency (LF≤1 Hz; LF-rTMS). These frequencies can either stimulate or inhibit the function of the cerebral cortex. rTMS can inhibit or stimulate unilateral brain function by regulating inter-hemispheric imbalanced inhibition. LF-rTMS was often used to inhibit the contralesional, unaffected hemisphere. HF-rTMS was often used to stimulate the ipsilesional, affected hemisphere (16). Both LF-rTMS and HF-rTMS were effective in the rehabilitation of motor dysfunction (17). The definite advantage of rTMS lies in its greater efficacy when applied during the acute and subacute phases, but not the chronic phase (18). Theta burst stimulation (TBS) is another mode of rTMS. It can efficiently reduce the stimulating time from 30 to 3 min. TBS uses two distinct stimulation methods: intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS).

4.1.1 RTMS on upper limb function rehabilitation in stroke

Both LF-rTMS and HF-rTMS improved upper limb function in stroke patients in most of the studies, and it was interesting to note that LF-rTMS was more effective in contralesional, unaffected hemisphere compared with HF-rTMS in ipsilesional, affected hemisphere (19, 20). Most trials had two common points: combined therapy and small sample size. It made the effect of rTMS alone unclear (21, 22). Yuan et al. also highlighted that the protocol design of rTMS needed to be standardized to further clarify effectiveness. Although the independent validity of rTMS could not be confirmed, a meta-analysis revealed that combining physiotherapy with another rehabilitation therapy, such as a combination of occupational therapy and rTMS, yielded effectiveness (23). The combination of two physical therapies, viz., LF-rTMS and functional electrical stimulation could improve finger mobility and grip ability in chronic stroke patients (24); and the combination of LF-rTMS with neuromuscular electrical stimulation could improve upper limb function in the acute stage of stroke (25).

The use of LF-rTMS on the contralesional primary motor cortex was effective for hand motor recovery in the post-acute stage of stroke. This therapy reached level A evidence (18). Furthermore, patients with stroke who received rTMS in the acute stage were found to have improved upper limb function for more than 1 year at follow-up in a randomized study (26). Spasticity is another dysfunction of the upper limb following a stroke. Some researchers focused on it with rTMS. The effect of rTMS on the improvement of spasticity in stroke patients was controversial. The result of one meta-analysis showed no conclusive evidence of improvement in spasticity with rTMS (27). Most of the trials that showed improvement in spasticity were combined therapy (28, 29). For example, rTMS was combined with occupational therapy or repetitive facilitative exercise. RTMS was mostly used as a single therapy in trials that showed little therapeutic effect (30–32).

In brief, LF-rTMS is a good choice for hand motor recovery in the post-acute stage of stroke. Further research is needed to identify more optimal combination therapies through trials

TABLE 3 The 10 most productive authors and the top 10 co-cited authors with the highest citations.

Rank	Author	Country	Counts	Citations	Co-cited author	Country	Co-citations	Centrality
1	Abo, Masahiro	Japan	54	1,080	Nitsche, Ma	Germany	1,258	0.07
2	Fregni, Felipe	USA	53	4,973	Liepert, J	Germany	1,123	0.06
3	Pascual-Leone, Alvaro	USA	50	5,361	Rossini, PM	Italy	1,049	0.10
4	Jang, Sung Ho	South Korea	48	589	Ziemann, U	Germany	943	0.04
5	Byblow, Winston D.	New Zealand	46	3,280	Di Lazzaro, V	Italy	915	0.04
6	Cohen, Leonardo G.	USA	46	4,425	Ward, NS	UK	868	0.06
7	Stinear, Cathy M.	New Zealand	42	3,470	Khedr, EM	Egypt	866	0.10
8	Kirton, Adam	Canada	34	1,035	Fregni, Felipe	USA	799	0.09
9	Rothwell, John C.	UK	31	3,689	Stinear, CM	New Zealand	794	0.04
10	Kakuda, Wataru	Japan	31	894	Lefaucheur, JP	France	746	0.06

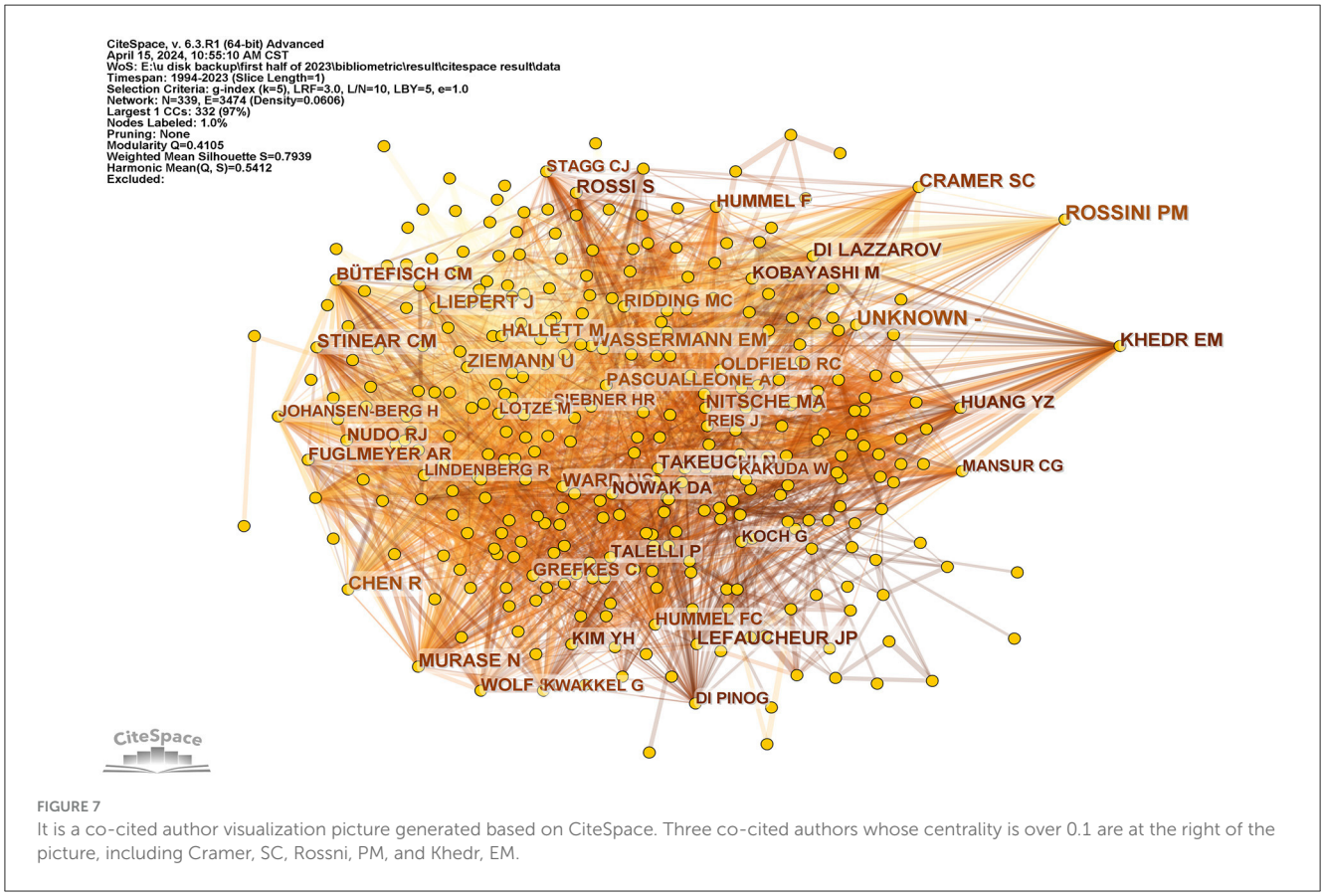

FIGURE 7
It is a co-cited author visualization picture generated based on CiteSpace. Three co-cited authors whose centrality is over 0.1 are at the right of the picture, including Cramer, SC, Rossni, PM, and Khedr, EM.

or meta-analyses. It remains unclear whether rTMS affects the improvement of spasticity in stroke patients.

4.1.2 RTMS on lower limb function rehabilitation in stroke

Several meta-analyses have shown that rTMS could improve lower limb motor function in stroke patients (21, 33–35). LF-rTMS could improve spatial gait symmetry when applied for 10 sessions over a period of 2 weeks (36), and HF-rTMS could improve walking speed compared to LF-rTMS (37). There were several types of combined therapy, such as a combination of HF-rTMS or LF-rTMS with transcranial direct current stimulation (tDCS) (38, 39), a combination of LF-rTMS and motor relearning procedure (40), and a combination of HF-rTMS and treadmill training (41). These combined therapies were effective. However, it remained unclear which combined therapy was more effective. A meta-analysis also showed that tDCS was superior to rTMS in improving lower limb motor function except for the combined therapy (42).

RTMS might be effective in the recovery of lower limb function after stroke. It reached level B evidence in the guidelines (18). It was also noted that TBS was not recommended in terms of motor

TABLE 4 The top 10 journals related to the research of TMS in stroke.

Rank	Journal title	Country	Counts	IF	JCR	H-index	Total citation
1	Neurorehabilitation and Neural Repair	USA	139	4.2	Q1	121	7,529
2	Clinical Neurophysiology	UK	128	4.7	Q2	200	10,544
3	Frontiers in Neurology	Switzerland	110	3.4	Q2	91	1,326
4	Frontiers in Human Neuroscience	Switzerland	99	2.9	Q3	144	2,886
5	Restorative Neurology and Neuroscience	Netherlands	97	2.8	Q3	83	3,597
6	Stroke	USA	69	8.4	Q1	343	9,724
7	Brain Stimulation	USA	66	7.7	Q1	99	3,803
8	Frontiers in Neuroscience	Switzerland	64	4.3	Q2	144	560
9	Experimental Brain Research	Germany	60	2	Q4	182	3,207
10	Brain	UK	50	14.5	Q1	365	10,128

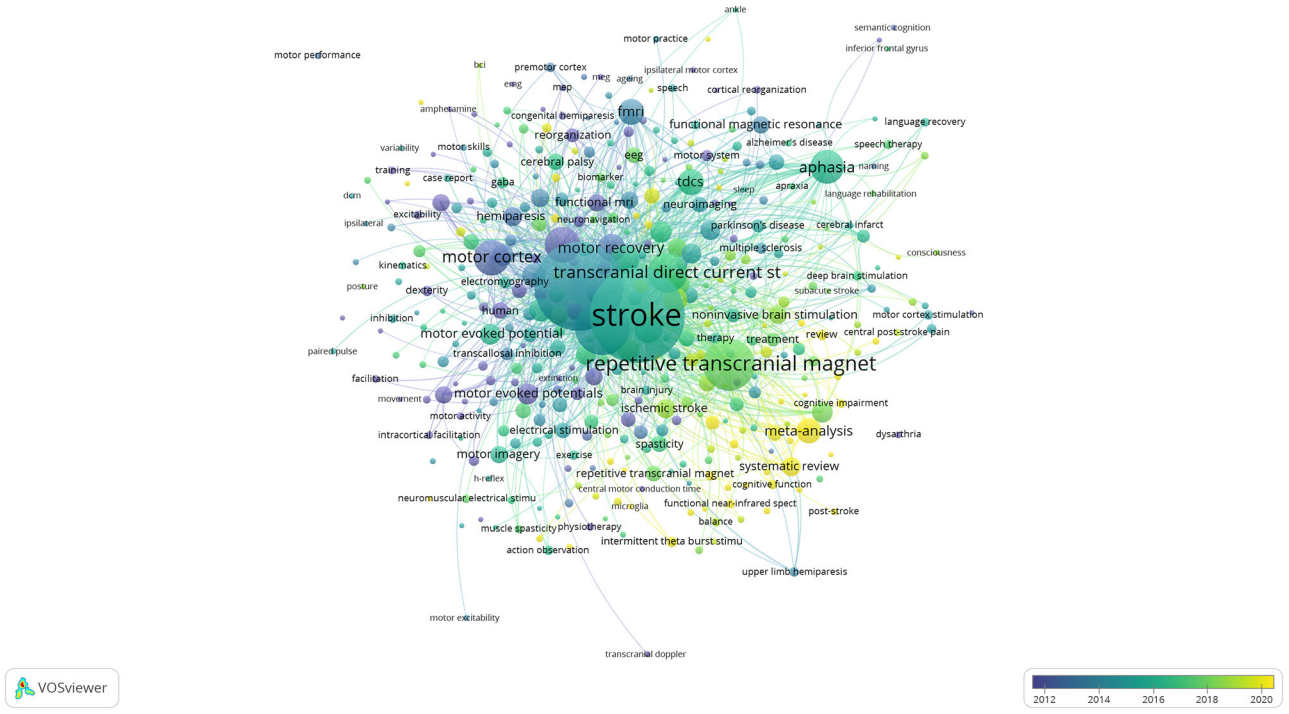

FIGURE 8
Overlay visualization map of keywords generated based on VOSviewer.

rehabilitation of stroke patients (18). Balance and ataxia are other important aspects of lower limb motor function. A preliminary study of LF-rTMS showed that 1 Hz rTMS over the cerebellum was safe (43). In subsequent studies, there was no clear and reliable evidence of whether rTMS could improve ataxia and balance after stroke in subsequent studies. However, we should be aware that a previous meta-analysis highlighted that tDCS was superior to rTMS in treating cerebellar ataxia (44).

In short, rTMS may impact lower limb recovery in stroke patients. Further research may reveal its impact on balance and ataxia, either in combination with other therapies or as a standalone treatment.

4.1.3 RTMS on post-stroke aphasia

A 12-month, small-scale, and placebo-controlled trial showed that LF-rTMS had potential clinical application value in treating aphasia after stroke in 2011. The course of therapy was 10 days. The results mainly showed that LF-rTMS could improve naming, expression, and understanding abilities (45). Subsequently, a randomized, double-blind study also showed that LF-rTMS could improve the condition of patients with severe aphasia when applied to the right hemisphere's frontal language area, and the duration of the therapy was 20 days (46). The assessment was conducted 15 weeks after completing the therapy. It further suggested that rTMS could improve non-fluent aphasia after stroke in a 2017

meta-analysis (47). However, three randomized controlled trials indicated that LF-rTMS did not improve post-stroke aphasia in the short term (2–4 weeks) in 2019 (48–50). Several meta-analyses have shown that rTMS could improve post-stroke aphasia regardless of being combined with other treatments (50–54). These conclusions should be treated with caution due to the high heterogeneity and the lack of high-quality evidence. Therefore, controlled trials of rTMS in post-stroke aphasia with large samples and long observation periods were urgently needed (55, 56).

In brief, rTMS in post-stroke aphasia is promising, and a long duration of observation is needed. A large-scale, randomized, and controlled trial is needed to assess the effects of rTMS on post-stroke aphasia.

4.1.4 RTMS on post-stroke dysphagia

The available results suggested that rTMS had a positive effect on post-stroke dysphagia (57–60), and HF-rTMS was usually chosen as therapy compared with LF-rTMS (61–64). The cerebellum is a common site to stimulate dysphagia. A randomized trial showed that rTMS combined with neuromuscular electrical stimulation could improve dysphagia in stroke patients and found that bilateral rTMS stimulation was better than unilateral stimulation (65). It differs from how rTMS treats motor dysfunction after stroke, which gives unilateral stimulation. However, a meta-analysis highlighted that there were still controversies about the best frequency and stimulated hemisphere (66). Bilateral cerebellar rTMS promoted the corticobulbar motor pathway to a greater extent than unilateral stimulation (67, 68). It was also found that unilateral and bilateral cerebellar stimulation of 10 Hz HF-rTMS could improve swallowing function by an observation of the treatment of dysphagia in brain-stem stroke patients. Bilateral stimulation could stimulate the excitability of the corresponding cortex more highly (61). Another sham-controlled double-blind trial showed that bilateral cerebellar stimulation with HF-rTMS improved dysphagia after stroke (69). Another single-blind randomized trial showed that 10 Hz rTMS at the bilateral motor cortex over the cortical areas projecting to the mylohyoid muscles was effective for dysphagia after stroke (70). It appears that rTMS holds more promise for dysphagia than for aphasia.

In recent years, TBS-related research in the field of stroke has gradually increased. A study found that iTBS could promote the excitability of the swallowing motor cortex and increase the connectivity of multiple brain regions in 2020 and might have therapeutic potential in treating dysphagia (71). A randomized controlled trial of 70 people showed that iTBS could improve dysphagia after stroke by stimulating the bilateral cerebellum, and it was safe in 2022. However, the effect mentioned in the article was better than rTMS, which remained to be verified (72). Another 47-person randomized controlled trial used HF-rTMS as the control group and found that there was no significant difference in clinical improvement and safety between iTBS and HF-rTMS. It suggested that iTBS might replace HF-rTMS in the field of dysphagia after stroke due to its efficiency in the same year. This trial also showed that iTBS was more effective than cTBS in improving dysphagia after stroke (73). However, the effectiveness still needed to be treated with caution due to a limited number of studies and heterogeneity (74).

In short, rTMS in the field of post-stroke dysphagia remains an area of significant interest. Dysphagia appears more promising for treatment with rTMS than aphasia, which may require a longer observation period for accurate assessment. It is suggested that either HF-rTMS or iTBS be selected to stimulate bilateral cerebellar regions. A large sample, randomized, and controlled trial should be conducted to determine the optimal combined therapy, which still needs to be further explored. Additionally, the long-term clinical effects and safety of rTMS for post-stroke dysphagia need to be further observed, as the optimal parameters and course of the treatment with rTMS remain uncertain.

4.1.5 RTMS on post-stroke cognitive impairment patients

Vascular cognitive impairment (VCI) is the cognitive impairment caused by cerebrovascular diseases. Post-stroke cognitive impairment (PSCI) is one type of VCI. PSCI is also a hotspot, as shown in Figure 8. Therefore, this article also summarized the research of rTMS in the field of PSCI over the past 5 years.

A study found that 5 Hz rTMS and iTBS could both improve PSCI, and the effect of rTMS was more effective than iTBS as early as 2020 (75). A retrospective study in 2022 found that stimulation of the dorsal prefrontal cortex (DLPFC) on the ipsilesional, affected hemisphere using HF-rTMS (20 Hz) resulted in better cognitive improvement in patients compared with a blank control group (76). Subsequent trials showed that iTBS could improve cognitive dysfunction in stroke patients (77, 78). These trials all showed the same characteristic: small sample size. The results of several meta-analyses have confirmed the therapeutic effect of rTMS in PSCI; however, the recommended methods were controversial (79–82). Wang et al. believed that both LF-rTMS and HF-rTMS were effective for PSCI, and the combined use of LF-rTMS and HF-rTMS was more effective. ITBS was not superior to rTMS in effectiveness (83). Liu et al. believed that iTBS was the first choice and HF-rTMS was the second choice in improving PSCI and activities of daily living (ADL) (79).

On the contrary, Yang et al. concluded that HF-rTMS was preferred for improving cognitive impairment and ADL (84). It was suggested that both HF-rTMS and LF-rTMS effectively improved attention and memory impairments in PSCI patients but there was no significant difference between them (81, 85, 86). However, a meta-analysis indicated that rTMS combined with cognitive training did not improve memory impairment (87).

The efficacy of rTMS on PSCI exists based on the above results. However, the optimal stimulation mode and parameters for different cognitive impairments, such as memory and attention, have not yet been determined. It is possible that HF-rTMS and LF-rTMS are both effective in treating PSCI. However, the current results cannot confirm whether there is a difference in efficacy between iTBS and rTMS due to the heterogeneity.

In brief, rTMS for PSCI is a significant area of research with two main key issues: (1) the comparative efficacy of iTBS, HF-rTMS, and LF-rTMS as stimulation modes; (2) the definitive impact of rTMS on PSCI. Therefore, we advocate for larger-scale, randomized controlled trials to assess these methods and their safety in the future.

4.2 Bibliometric analysis of TMS in stroke

Scholars are expected not only to have a deep comprehension of their research field but also to maintain a broad understanding of evolving trends and interdisciplinary connections in today's era of big data. Bibliometrics provides comprehensive visualization and analysis, tracking the advancement of research across various fields. Furthermore, bibliometric analysis facilitates the exploration of emerging research areas and the identification of hotspots. It aids researchers in comprehensively and rapidly learning about the progress in TMS related to stroke. Moreover, it can indicate the direction for future research endeavors.

4.2.1 The popularity of TMS research in the stroke field continues; the United States has the largest number of articles in this field

Research on TMS in the field of stroke has exhibited a significant rise in the number of publications between 1994 and 2023. Figure 2 shows the annual number of publications. It increased from 5 articles in 1994 to 314 articles in 2022. There were five articles in 1994 in the WoS core collection. The most highly cited publication from that year was Schnitzler and Benecke (88), with 111 citations, which was the highest among the 5 publications (88). The findings of this article also supported the notion that the silent period (SP) induced by TMS originated in the primary motor cortex. It provided theoretical support for the current treatment of stroke-related disability using TMS.

Although there were declines in the number of articles in adjacent years (2008–2009, 2017–2018, and 2022–2023) in Figure 2, the overall trend still indicated an increasing number of publications. Figure 3 illustrates that the application of TMS in stroke initially originated in Europe, particularly in Germany and the United Kingdom before gradually expanding to the United States and other countries in the Americas. The number of relevant articles published by China has significantly increased, indicating a literature burst since 2020. According to Table 1, the United States has published the most (953 articles), closely followed by China (546 articles). This indicated that although China started later than others, it has been actively engaging in more pertinent research in recent years.

4.2.2 Harvard University had the most articles on TMS in the field of stroke

Four institutions, including Harvard University, NINDS, Emory University, and Northwestern University, are located in the United States. Three institutions are located in Europe (University College London, the University of Manchester, and University Tubingen). Two institutions are located in Asia (Yeungnam University and JiKei University). One institution is located in Oceania (University of Auckland) and is among the top 10 institutions that have made contributions. Four institutions in the United States specialized in using TMS in stroke research, as previously shown in Table 2. The institution with the largest proportion of articles was Harvard University (138 articles, 12,813 citations). It accounted for 19.1% of the total national publications and 24.3% of the total national citations. The remaining 3 institutions were NINDS with 65 articles. Emory University has 61 articles, and Northwestern University has 58 articles. Table 2 and Figure 6 highlight two institutions, namely, Harvard University and University College London, with centrality >0.1. It indicated that these two institutions played a pivotal role and were potential partners for other institutions in this field. China (402 articles) ranked second in the country of publication. However, no Chinese institution published more articles than the University of Manchester, which had 58 articles ranked 10th. This might be due to the involvement of many research institutions in China, each publishing a relatively small number of articles.

The search result showed that Harvard University had published 81 articles over the past 10 years (2014–2023). TMS was used as a therapy for motor recovery (37, 89, 90). Furthermore, these results suggested that rTMS might effectively improve motor function. However, the results of Harvey et al. showed no significant improvement in upper limb function after stroke. This might be because the intervention was not conducted during the acute stage of stroke when rTMS is more effective. In addition, two studies demonstrated the safety of rTMS application on stroke patients and its potential to improve motor function (91, 92).

In brief, Harvard University's research in the field of TMS has been extensive. The sample is larger and of higher quality, making it suitable for new researchers to learn from. However, the number of related articles has been decreasing in recent years.

University College London published 68 articles between 2014 and 2023, during which TMS was primarily used to evaluate stroke neuropathology (93–97). In addition, it also provided theoretical support for the treatment of post-stroke dysphagia and aphasia with rTMS. Sasegbon et al. hypothesized that stimulating the bilateral cerebellar pathway with rTMS was more effective than a unilateral approach for post-stroke dysphagia. The result showed that an increase in cortical excitability associated with pharyngeal movements when 10 Hz rTMS stimulated the cerebellum bilaterally or unilaterally (67, 98, 99). This was a reason for the increase of rTMS research on post-stroke dysphagia in recent years. Therefore, TMS has the potential to be used as a therapy for dysphagia. The reference with the most citations from University College London was "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)" in 2014. This article summarized the various fields of rTMS application and provided evidence for the effect on dysfunction or disease. There was another updated version in 2020, and the details were discussed in Section 4.1.

NINDS and the University of Tubingen experienced the earliest literature burst. They concentrated around 2010 as shown in Figure 5 followed by Harvard University, University College London, and University Manchester. This also indicated that the United States made rapid progress in this field. In recent years, literature burst in this field primarily focused on China. Sun Yat-sen University was one of the representatives.

Sun Yat-sen University has published a total of 50 articles. Most of them have focused on the field of post-stroke dysphagia and aphasia over the past 10 years. The main research findings were as follows. A single-blind randomized controlled trial showed that 10 Hz HF-rTMS delivered under the cerebellum could improve infratentorial stroke dysphagia (68). Another randomized, double-blind, controlled trial showed iTBS could

also improve post-stroke dysphagia (72). A study showed that 5 days might be the shortest treatment duration for post-stroke dysphagia (66). In addition to clinical trials, there were studies on the mechanism of rTMS in stroke therapy. As early as 2017, some studies highlighted that HF-rTMS could be used to improve functional recovery in patients with ischemic stroke by enhancing neurogenesis and activating brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase B (TrkB) signaling pathways (100). RTMS could modulate microglia with anti-inflammatory polarization variation. It could also promote neurogenesis and the proliferation of neural stem cells in subsequent studies for ischemic stroke (101, 102). For the mechanistic study of dysphagia, two studies showed that HF-rTMS could modulate the composition of gut microbiota and improve aspiration-induced pneumonia caused by dysphagia (103, 104). In short, if an individual is interested in rTMS in the therapy of post-stroke dysphagia, they may follow the work of Sun Yat-sen University.

4.2.3 The cooperation between the authors from different countries needs to be further strengthened

Among the top three productive authors listed in Table 3, only Abo, Masahiro is from Japan, while, Fregni, Felipe, and Pascual-Leone, Alvaro, are from the United States. Abo, Masahiro's research has primarily focused on clinical research in this field over the past 3 years. "NEURO" was the recommended therapy in these trials, where LF-rTMS was combined with one-on-one intensive occupational therapy. The advantage of this combination therapy was its ease of implementation. The results of several retrospective studies showed that "NEURO" therapy was helpful for upper limb functional recovery after stroke. The effect of recovery was related to the severity of the stroke (105, 106). The mechanism of LF-rTMS combined with occupational therapy enhanced the functional roles of networks in motor-related areas of the ipsilesional cerebral hemisphere in the latest study (107).

Additionally, other studies have shown that the application of HF-rTMS in the acute phase of stroke is safe (108, 109). A literature study focused on the use of HF-rTMS in combination with intensive speech-language-hearing therapy for aphasia. It was found that HF-rTMS combined with speech therapy had a positive effect on both fluent and non-fluent aphasia. However, the results require further validation through studies with large sample sizes (110). It should be noted that Abo, Masahiro's clinical studies had small sample sizes (<100 people on average). His research team also developed a protocol in 2022 (111) indicating the need for a large, multicenter, controlled study in this field. However, the related article has not yet been published.

In summary, Abo Masahiro's team has conducted in-depth research on rTMS in combination with occupational therapy. This combined therapy is very suitable for rehabilitative therapists or hospital clinical practitioners to carry out and observe the results. These results are also very suitable for new researchers to learn about, but the drawback is that the independent effects of rTMS cannot be observed.

Fregni, Felipe is affiliated with Harvard University. Fregni, Felipe conducted a TMS study with fewer publications in recent years compared to Abo Masahiro. Fregni, Felipe demonstrated using TMS as a single therapy often and combined therapy less frequently to observe the results in the experimental design. Furthermore, the sample size of Fregni, Felipe's team was larger in this field than Abo Masahiro. Interestingly, Fregni designed a study to investigate biomarkers associated with functional disability in a 2021 protocol article. The study utilized evaluation tools such as TMS electroencephalograms, functional near-infrared spectroscopy, and magnetic resonance imaging. The content is worth paying attention to in the future (112).

Compared with Fregni, Felipe, Pascual-Leone, Alvaro has published fewer relevant articles in recent years. There were mainly three related studies, all published in 2016. One study evaluated the improvement of assisted robots in stroke patients with rTMS (113). The other two studies explored the effects of LF-rTMS and HF-rTMS on motor function in stroke patients. The results also indicated that LF-rTMS could enhance cortical excitability and the response of the affected hand in the ipsilateral hemisphere (92). HF-rTMS intervention should be individualized based on functional corticospinal tract status and brain-derived neurotrophic factor genotype to improve the upper extremity motor of patients with stroke (114).

Although Abo, Masahiro published the most articles, with 52 articles and 1,002 citations, the citations were significantly lower than those of Fregni, Felipe (4,776 citations) and Pascual-Leone, Alvaro (5,151 citations). The centralities of individual authors are <0.1. This indicates that authors should enhance collaboration between countries.

It could be observed from Table 3 that two authors, Rossini, PM, and Khedr, EM, had centrality values >0.1 in terms of co-citation. The co-citations of Khedr, EM's literature did not reach those of Rossini, PM. Khedr, EM mostly focused on LF-rTMS or HF-rTMS in stroke patients' motor function recovery (115–118) and dysphagia (119–121). Rossini, PM (122, 123) had few studies published in this area. His relevant articles served as guidelines for the clinical application of rTMS, which might also explain its high centrality (135).

4.2.4 The United States accounts for the largest proportion of the top 10 publications in this field

Three publishing houses are based in the USA, and two are located in the UK. Three publishing houses are located in Switzerland. One publishing house is in the Netherlands and the other in Germany. There are three publishing houses located in quartile one of the JCR divisions: *Neurorehabilitation and Neural Repair*, *Stroke*, and *Brain Stimulation*. There are three in quartile two, including *Clinical Neurophysiology*, *Frontiers in Neurology*, and *Frontiers in Neuroscience*. There are two in quartile three: *Frontiers in Human Neuroscience*, *Restorative Neurology, and Neuroscience*. The remaining publishing house is located in quartile four: *Experimental Brain Research*. A total of 882 articles were published, with American publishing houses contributing the largest share, accounting for 31.1% of the top 10 publishing houses' outputs. The journal *Brain* had the highest impact factor among the top 10 journals. It had an impact factor score of 14.5 points. The remaining nine journals did not exceed 10 points; their H-index reached 365. However, only 50 articles were included. The research

TABLE 5 The top 20 keywords with the highest frequency related to the research of TMS in stroke.

Rank	Keyword	Occurrence	TLS	Rank	Keyword	Occurrence	TLS
1	Stroke	1,275	4,070	11	Neurorehabilitation	109	398
2	Transcranial magnetic stimulation	1,119	3,392	12	fMRI	96	350
3	Rehabilitation	420	1,494	13	tdcs	95	353
4	Repetitive transcranial magnetic stimulation	384	1,128	14	Meta-analysis	93	310
5	Transcranial direct current stimulation	225	773	15	Non-invasive brain stimulation	87	300
6	Motor cortex	182	602	16	Neuromodulation	84	300
7	Plasticity	179	631	17	Cortical excitability	80	291
8	Aphasia	160	551	18	Recovery	80	166
9	Neuroplasticity	117	436	19	Stroke rehabilitation	78	235
10	Motor recovery	113	393	20	Motor function	69	259

content in the Journal *Brain* was mostly neurophysiological research after stroke. TMS was used as an assessment. Some studies highlighted that there was a disinhibition of the motor cortex in the unaffected hemisphere and an exaggeration of inhibition in the affected hemisphere after a stroke (124, 125). Through 2 years of observation, Classen et al. found that when TMS was applied to stimulate the contralateral hand muscles of the affected hemisphere, it resulted in an SP extension and a normal evoked potential. Hyperactivity of cortical inhibitory interneurons might be the reason for the motor dysfunction observed in stroke patients. Netz et al. found that the TMS in affected or unaffected hemispheres could extend the SP, and motor output was reorganized in the non-affected hemisphere. However, Netz et al. did not consider this reorganization of motor output to be clinically improved (126). Another study also noted that cortico-bulbar tract fibers were involved in dysarthria after stroke (127). This is also a referential location to stimulate TMS for dysfunction after stroke, such as dysphagia and aphasia. Hummel et al. (128) did not propose TMS as a rehabilitation treatment for stroke until 2005 in the Journal *Brain*. The results also mentioned that TMS might be used as an adjunct to neurorehabilitation. However, this did not mean that Hummel, F. was the first to introduce TMS into the field of stroke rehabilitation. There were five articles included in 2012. However, the number of literature included decreased, with an average annual inclusion of 1.45 articles (2013–2023).

There were 65 related articles in the journal *Stroke*, whose impact factor ranked second, and the content was mostly related to the prognosis of TMS in the therapy of stroke. The study by Traversa et al. highlighted that there was plasticity after central nervous system injury in adults and that the plasticity could persist for 2–4 months (129). A study suggested that inter-hemispheric asymmetry of the motor cortex was associated with stroke recovery, which was a mechanism for rTMS in stroke (130). It was found that TMS could induce motor evoke potential (MEP) in stroke patients, and MEP had been proposed to have a prognostic effect (131, 132). MEP has also been used in subsequent TMS-related studies. In short, these findings provide a theoretical basis for studying TMS in stroke.

The earliest article applying transcranial magnetic stimulation (TMS) technology to stroke rehabilitation, authored by Arac et al. in 1994, primarily explored the prognostic value of TMS in stroke treatment. The outcome of this study was negative, which can be attributed to the fact that repetitive TMS (rTMS), as it is used today, had not yet been fully developed for stroke rehabilitation at that time. To validate our findings, we conducted an extensive search within the Web of Science (WoS) database, including all relevant databases and collections, dating back to 1988. The first research result related to TMS therapy for stroke remains the study by Arac et al. (133). Notably, six articles in this field were published in 2006 in the journal *Stroke,* and the average annual number of articles published in the past decade (2013–2023) was 2.7.

4.2.5 Three articles have played significant roles in the field

The most citations were 1,578 times, and the least were 794 times. It was noteworthy that the top three articles, all published after 2010, were guidelines: Langhorne et al. (7), Winstein et al. (134), and Lefaucheur et al. (123). The most cited article was by Langhorne et al. (7). In the article by Langhorne et al. (7), TMS was applied in stroke rehabilitation, and the authors acknowledged that it was still uncertain whether these interventions enhanced functional outcomes. There might be advancements in combination therapy in these fields. It was confirmed that combination therapy was effective in Winstein et al. (134). The article noted that brain stimulation technology, including TMS, could have therapeutic effects when combined with behavioral or language therapy. This could explain why aphasia has become a therapeutic hotspot for rTMS treatment in recent years. It should be noted that Winstein et al. (134) had 1,349 citations, while the publication date was as recent as 2016.

4.2.6 The applications of rTMS in dysphagia and cognitive impairment of stroke may be future hotspots

As shown in Table 5, the top three keywords with the highest frequency of occurrence based on this search query string were as follows: “stroke” (1,119 times), “transcranial magnetic stimulation” (1,030 times), and “rehabilitation” (387 times). The frequency

of "rehabilitation" was significantly lower than that of the first two keywords. It could be observed that the peak period for the keywords "stroke" and "TMS" was relatively close, occurring around 2014, as shown in Figure 8. Subsequently, the research focus shifted to rTMS (around 2016), which was mostly used for motor recovery, aphasia, and dysphagia in stroke patients. In recent years, the focus of research has included rTMS therapy for aphasia and dysphagia. It was found that 335 articles were retrieved using "aphasia" as the keyword in the search results. The average number of relevant articles published per year was 23.5 over the past 10 years (2013–2023). Most of the articles were published in 2022 (28 articles). When dysphagia was retrieved as a keyword, it could be observed that the number of relevant articles was significantly lower than that of aphasia (166 articles). However, surprisingly, there was an explosive growth in the number of relevant articles in 2022 (38 articles). It was the year with the highest number of articles published on dysphagia following a stroke. The number of articles on dysphagia surpassed that on aphasia (2021–2023). This indicated that dysphagia has been emerging as a research hotspot in the field of stroke rehabilitation over the past 3 years (2021–2023). Thus, treatment of dysphagia may be a hotspot by rTMS in the future.

Research in the field of cognitive impairment related to stroke has been increasing in the last 3 years, as shown in Figure 8. This trend indicated that treating PSCI by rTMS may be another hotspot. The related literature volume was up to 103 articles. The type of article included protocols, clinical observations, and meta-analysis. The details are discussed in Section 4.1.5.

5 Conclusion

In summary, TMS research in the field of stroke continues to be active and promising, with the United States leading in the number of published articles at 953. Harvard University and University College London have demonstrated significant betweenness centrality, highlighting their pivotal roles and potential as key collaboration partners. Strengthening author cooperation across countries is advisable. TMS applications for post-stroke cognitive impairment, aphasia, and dysphagia are emerging as research hotspots with promising prospects. Combining rTMS with occupational therapy may offer potential benefits for upper limb recovery after a stroke. Identifying more effective combined therapies with rTMS remains a priority. Future research should focus on large-scale, randomized, and controlled trials to address these post-stroke dysfunctions.

6 Limitations

There are some limitations to our study. First, it takes a certain amount of time for an article to achieve a certain number of citations. High-quality literature needs to take time to reach the expected citations. Second, VOSviewer does not list the affiliated organization and the WoS division organization is more detailed than VOSviewer. As a result, the overall statistical results of VOSviewer are lower than the actual data and the synonym replacement function cannot be completely covered. Therefore, the corresponding statistical data shall be subject to the data displayed in WoS. Third, we limited our analysis to English language articles, which may have led to the exclusion of non-English high-quality literature. Finally, in the author analysis, we did not distinguish between the first author and other authors, which could have affected the interpretation of the author's impact.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

X-YL: Writing – original draft, Writing – review & editing, Visualization. RH: Conceptualization, Writing – review & editing. T-XL: Project administration, Supervision, Validation, Writing – review & editing. YL: Data curation, Validation, Writing – review & editing. LD: Data curation, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1424545/full#supplementary-material

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A systematic review of post-stroke fatigue measurement scale based on COSMIN guidelines

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Objective: This study aimed to evaluate the methodological quality and measurement attribute quality of the post-stroke fatigue measurement scale, so as to provide some basis for the clinical application and promotion of related scales.

Methods: The Chinese National Knowledge Infrastructure, the Wanfang Data Knowledge Service Platform, the China Science and Technology Journal Database, the Chinese Medical Journal Full-text Database, the Chinese Biology Medicine, PubMed, Embase, Medline, the Cochrane Library, the Web of Science, CINAHL, and PsycINFO databases were searched for literature on the post-stroke fatigue measurement scale up to June 2022. Literature screening and data extraction were carried out independently by two researchers, and in the case of disagreement, discussions were held with a third investigator to reach an agreement, and the COSMIN checklist and criteria were used to systematically evaluate the attributes of the measurement scale.

Results: A total of 17 studies were included, involving 10 post-stroke fatigue measurement scales. The content validity of FSS-7, FACIT-F, NRS-FRS, and MFI-20 was "not mentioned," and the remaining scales were "uncertain." In terms of construct validity, MFS was "adequate"; FSS-7, FACIT-F, and NRS-FRS were "not mentioned"; and the remaining scales were "uncertain." In terms of internal consistency, NRS-FRS was "not mentioned"; FSS and MFS were "adequate"; and the remaining scales were "uncertain." In terms of hypothesis testing, CIS and FACIT-F were "not mentioned," NRS-FRS was "adequate," and the remaining scales were "uncertain." The stability of FSS-7, CIS, FACIT-F, and MFI-20 was "not mentioned," and the remaining scales were "adequate." The cross-cultural validity of FSS-7 was "adequate," and the remaining scales were "not mentioned." All 10 scales were given a recommendation grade of "B".

Conclusion: For the time being, the FSS can be recommended to measure post-stroke fatigue, but it still needs to be tested for more relevant measurement properties in order to gain more support from high-quality evidence. For a more comprehensive assessment of post-stroke fatigue, the FIS, FAS, and NFI-stroke should perhaps be considered, as the FSS is a one-dimensional scale that can only measure physical fatigue in patients; however, these scales also need to be tested for more relevant measurement properties to verify their clinical applicability.

KEYWORDS

post-stroke fatigue, measurement scales, COSMIN guide, systematic review, fatigue severity scale

1 Introduction

Post-stroke fatigue is not related to tension and is a subjective feeling of stroke survivors about weakness and tiredness (1, 2). PSF arises not only from physical activities but also from mental or social activities. As one of the common complications after stroke, it has a high incidence, which will make it difficult or impossible for patients to maintain daily activities, thus causing a certain degree of adverse effects on their quality of life (3, 4). Accurate measurement of PSF is the premise and basis for the timely and effective treatment of the disease. There are many scales used to measure PSF, such as the fatigue severity scale (FSS) (5), fatigue impact scale (FIS) (6), and fatigue assessment scale (FAS) (7). Kjeverud et al. (8) explored the frequency and overlap of PSF by using scales, such as FSS, and the results showed that different scales produced different results. Blackwell et al. (9) noted that there are currently no corresponding guidelines to assess fatigue management in patients with PSF in fatigue management and that there are no established guidelines yet. Thus it can be seen different measurement focus of different scales, it has not been able to determine whether these scales have good measurement properties, and few studies to systematically evaluate these measurement properties. The guidelines for the selection criteria for health measurement tools (COSMIN) (10) can assess the methodological quality and measurement attribute quality of the scale, and the best scale for the purpose of the study can be selected. In this study, a systematic evaluation of PSF measurement scales using COSMIN quality standards was carried out to clarify the methodological quality and measurement attribute quality of relevant scales. It aimed to comprehensively evaluate the evidence level of each measurement attribute, leading to the final recommendation and providing certain evidence-based support for the application and promotion of relevant scales in clinical practice.

2 Materials and methods

2.1 Inclusion criteria and exclusion criteria

Inclusion criteria were as follows: ① study subjects were stroke patients; ② the study includes the measurement performance evaluation of the PSF measurement scale; ③ at least one measurement attribute was evaluated on the scale; ④ access to the full text of the Chinese and English literature, where nationality is not limited. Exclusion criteria were as follows: ① review, systematic evaluation, conference, animal experiments, qualitative research, cases, and other types of literature; ② the evaluation tool is only used to study the current status of its application and collect research subject data or the literature measuring outcome indicators.

2.2 Literature retrieval strategy

Literature on PSF measurement published from the database until June 2022 in the Chinese Journal Full-text Database, the Wanfang Data Knowledge Service Platform, the VIP Database, the Chinese Medical Journal Full-text Database, the Chinese Biomedical Literature Database, PubMed, Embase, Medline, the Cochrane Library, the Web of Science, CINAHL, and PsycINFO databases were being retrieved using a computer. The literature search was completed by the combination of subject words and free words, and the gray literature search was performed.

2.3 Literature screening and data extraction

Two researchers who had participated in the relevant training and fully mastered the COSMIN evaluation criteria independently completed the literature screening and data extraction according to the inclusion and exclusion criteria and cross-checked the results. Once a disagreement occurs, they discuss it with the third investigator to reach a consensus. The contents of data extraction include those as follows: the first author, year of publication, country, scale name, sample size, scale dimension, scoring method used for each item, scale evaluation time, and retest time.

2.4 Evaluation steps

Two investigators independently completed the quality of PSF, the quality of measurement attributes, and the level of evidence using the COSMIN risk of bias tool (10) and performed a cross-check. In the case of disagreement, they discussed it with the third investigator to reach an agreement. The contents of data extraction include those as follows: the first author, year of publication, country, scale name, sample size, scale dimension, scoring method used for each item, scale evaluation time, and retest time.

2.5 Study tools

2.5.1 Methodological quality evaluation

The methodological quality of the included scale was assessed according to the COSMIN risk of bias checklist (11). A total of 10 modules need to be evaluated, namely, content validity scale development, content validity, structure validity, internal consistency, cross-cultural validity or measurement invariance, stability, measurement error, validity and criterion validity, hypothesis testing, and responsiveness. The risk of bias of each item in the module was evaluated with the result of "very good" "adequate" or "doubtful" or "inadequate," and then the minimum evaluation of all the entries in a module was taken as the total evaluation result of the module.

2.5.2 Quality evaluation of the measurement properties

The quality of the nine measurement attributes of content validity, construct validity, internal consistency, stability, measurement error, hypothesis testing, cross-cultural validity or measurement invariance, criterion validity, and responsiveness were evaluated according to the COSMIN quality specification (12), and the evaluation rating is "sufficient (+)" or "inadequate (−)" or "uncertain (?)." When a measurement attribute of a scale is "sufficient (+)" or "inadequate (−)" or "uncertain (?)," the overall rating of this measurement attribute is also "full (+)" or "inadequate (−) "or "unsure (?)." In the meantime, when a measurement attribute of the scale is not evaluated consistently among studies, and the reason cannot be explained, then the overall rating of the measurement attribute is also "inconsistent (±)."

2.5.3 Evaluation of the evidence grade

The inclusion scale was assessed according to GRADE (13), evaluating it based on the risk of bias, inconsistency, imprecision, and indirectness. COSMIN first identified the measurement attributes of the measurement scale as "high quality," then downgraded according to the above four aspects, and divided the level of evidence into "high" or "medium" or "low" or "extremely low." Subsequently, opinions on the recommended strength of the scale were formed based on the evidence evaluation results. The recommended strength of the scale is "A" or "B" or "C"; "A" is recommended, "C" is not recommended, and "B" is between "A" and "C," indicating that the scale has some potential, but more studies need to be conducted to verify its effectiveness. The content validity of the recommended strength "Grade A" is "sufficient" and the internal consistency level is not "low"; "Grade C" is proven insufficient; and "Grade B" corresponds to neither "Grade A" nor "Grade C"

3 Results

3.1 Literature search results

In total, 774 articles were screened according to inclusion and exclusion criteria, and 17 articles were finally included. The literature screening process is shown in Figure 1.

3.2 Basic characteristics of the included literature

A total of 17 literature articles were included in this study (5–7, 14–27), involving 10 PSF-related measurement scales, namely, the Fatigue Severity Scale (FSS), Fatigue Severity Scale (7 entries) (FSS-7), Fatigue Impact Scale (FIS), Fatigue Assessment Scale (FAS), Stroke nerve fatigue Index Scale (NFI-Stroke), Personal Fatigue Strength Questionnaire (CIS), Functional Assessment of Chronic Disease Treatment-Fatigue Scale (FACIT-F), Digital Pain Scale-Facial expression Scale (NRS-FRS), Chinese version of Self-rating scale of mental fatigue (MFS), and The Chinese version of the multidimensional fatigue directory (MFI-20). Among them, the most evaluated scale was FSS with nine entries, while FSS-7 had two fewer entries with seven items. The NRS-FRS does not explicitly mention the scale dimensions, and FSS, FSS-7, and FACIT-F are all one-dimensional scales, while the rest are multidimensional scales. The scoring methods used for each item included Likert 4 scoring, Likert 5 scoring, and Likert 7 scoring; Likert 5 scoring was the most commonly used item scoring method in the included studies. The interval between the two measurements of the scale ranged from 2 days to 2 months. The basic characteristics of the included PSF correlation measurement scales are detailed in Table 1.

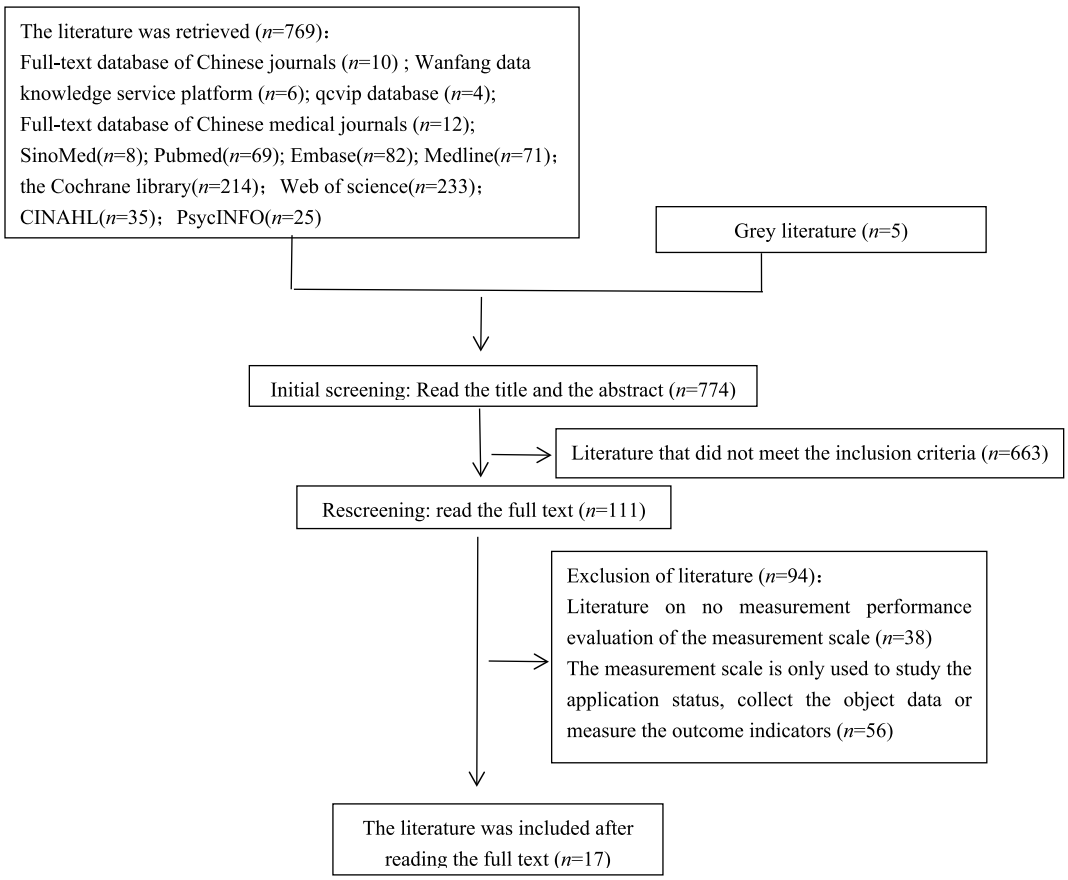

FIGURE 1
Flow chart of literature screening.

TABLE 1 The basic characteristics of the included PSF correlation measurement scales.

The first author	The year of publication	Country	Scale name	Sample size	Number of scale entries/ scale dimension	Scale dimension	Scoring method used for each entry	Time to scale completion (min)	Retest time
Chun-wei Wu (14)	2007	China	FSS	214	9/1	Fatigue consequences	Grade likert 7	NR	NR
Nadarajah M et al. (15)	2017	Malaysia	FSS	100	9/1	Fatigue consequences	Grade likert 7	NR	1 Week
Ozyemisci-Taskiran O et al. (5)	2019	Turkey	FSS	98	9/1	Fatigue consequences	Grade likert 7	NR	1 Week
Abdulla FA et al. (16)	2019	Saudi Arabia	FSS	217	9/1	Fatigue consequences	Grade likert 7	NR	1 Week
Lerdal A et al. (17)	2011	Norway	FSS-7	119	7/1	Fatigue consequences	Grade likert 7	NR	NR
Chun-wei Wu (14)	2007	China	FIS	214	40/3	Physical, cognitive, and social	Grade likert 5	NR	NR
Saneii S H et al. (6)	2020	Iran	FIS	280	40/3	Physical, cognitive, and social	Grade likert 5	10 ~ 20	1 Week
Batur EB et al. (18)	2021	Turkey	FIS	82	40/3	Physical, cognitive, and social	Grade likert 5	NR	1 Week
Smith OR et al. (19)	2008	Holland	FAS	377	10/2	Physical fatigue, mental fatigue	Grade likert 5	NR	Two months
Brårdal A et al. (20)	2016	Sweden	FAS	72	10/2	Physical fatigue, mental fatigue	Grade likert 5	NR	NR
Ho LYW et al. (7)	2021	China	FAS	112	10/2	Physical fatigue, mental fatigue	Grade likert 5	NR	7.22±0.51 days
Chen Hongmei et al. (21)	2020	China	NFI-Stroke	370	12/2	Body, cognition	Grade likert 4	NR	2 Weeks
Taasen I et al. (22)	2020	Norway	NFI-Stroke	66	12/2	Body, cognition	Grade likert 4	NR	2 Days to 1 week
Ho LY et al. (23)	2021	China	NFI-Stroke	177	12/2	Body, cognition	Grade likert 4	NR	7 ~ 10 Days
Chun-wei Wu (14)	2007	China	CIS	214	20/4	Subjective fatigue, attention, motivation, and physical strength	Grade likert 7	NR	NR
Butt Z et al. (24)	2013	America	FACIT-F	399	13/1	NR	Grade likert 5	NR	NR
Chuang LL et al. (25)	2015	China	NRS-FRS	106	NR	NR	NR	NR	1 Week
Liu Xiaoling et al. (26)	2018	China	MFS	295	15/4	Increased sensitivity, fatigue perception, cognitive fatigue, and altered sleep	Grade likert 4	NR	1 Week

(Continued)

TABLE 1 (Continued)

The first author	The year of publication	Country	Scale name	Sample size	Number of scale entries/ scale dimension	Scale dimension	Scoring method used for each entry	Time to scale completion (min)	Retest time
Chen Yiting et al. (27)	2022	China	MFI-20	374	20/6	Overall fatigue, attention fatigue, physical fatigue, mental fatigue, reduced activity, and decreased power	Grade likert 5	NR	NR

FSS, Fatigue Severity Scale; FSS-7, Fatigues Severity Scale (7 items); FIS, Fatigue Impact Scale; FAS, Fatigue Assessment Scale; NFI-Stroke, Stroke nerve fatigue refers to Quantity Scale; CIS, Personal Fatigue Strength Questionnaire; FACIT-F, Chronic disease treatment Functional Assessment-Fatigue Scale; NRS-FRS, Digital pain grading-facial expression Scale; MFS, Chinese mental fatigue self-rating scale; MFI-20, multidimensional fatigue scale; and NR, not mentioned.

3.3 Methodological quality and measurement attributes quality evaluation results

The 17 included papers (5–7, 14–27) evaluated the content validity, structural validity, internal consistency, hypothesis testing, stability, cross-cultural validity, or measurement invariance of the scales in terms of methodological quality and quality of measurement attributes. (1) Content validity: eight studies (6, 7, 14, 20–23, 26) completed the evaluation of the scale content validity by consulting with experts. However, due to the insufficient description of the evaluation methods and processes adopted by the experts, the methodology quality assessment is "fuzzy" and the content validity is "uncertain." Five studies (6, 7, 21, 23, 26) asked about patients' understanding of the content of the scale, and two studies (6, 7) conducted face-to-face interviews with the patients and adjusted the content of the scale based on the interview results, but the methodology quality was assessed as "good" and "good" while the content validity was "sufficient"; the other three studies (21, 23, 26) did not perform qualitative analysis, the methodology quality and content validity corresponded to "fuzzy" and "uncertain." (2) Structural validity: eight studies (5, 7, 14, 16, 21, 23, 26, 27) reported the test results of the structural validity of the scale. Among them, four studies (14, 16, 21, 27) used only the exploratory factor analysis to evaluate the structural validity of the scale, and the methodological quality was "good"; four studies (5, 7, 23, 26) performed confirmatory factor analysis, one study (5) was "good" due to insufficient sample size, and the other three studies (7, 23, 26) was "very good." Two studies (23, 26) also reported the comparative fit coefficient of the scale (0.97), thus its construct validity was "sufficient." (3) Internal consistency: 16 studies (5–7, 14–24, 26, 27) evaluated the internal consistency of the scale; of which, 8 studies (6, 15, 17–20, 22, 24) did not test the structural validity of the scale, the methodological quality corresponds to "fuzzy," another 8 studies (5, 7, 14, 16, 21, 23, 26, 27) in addition to containing the test results of structural validity, also includes the Cronbach's α coefficient of each dimension of the scale, thus the methodological quality is "very good." In one study (23), Cronbach's α coefficient is <0.7, its internal consistency corresponds to "inadequate." (4) Hypothesis testing: The methodological quality of 11 studies (5, 7, 15, 16, 18, 20, 21, 23, 25–27) was "good"; 2 studies (6, 17) failed measurement properties or statistical analysis methods. A total of 10 studies (5–7, 15, 17, 18, 21, 23, 26, 27) did not make the hypothesis test as "uncertain," and the (16, 20, 25) was "sufficient" in the remaining three studies. (5) Stability: 10 studies (5–7, 15, 16, 18, 20, 23, 25, 26) assessed the stability of the scale by test-retest reliability, of which 5 studies (7, 16, 18, 20, 23) were "fuzzy" in terms of methodological quality as they did not specify the measurement situation or retest time. In total, 10 studies (5–7, 15, 16, 18, 20, 23, 25, 26) all had a within-group correlation coefficient of >0.7, thus their stability was "sufficient." (6) Cross-cultural validity or measurement invariance: only one study (17) conducted differential item functioning (DIF) analysis and the results showed that there is no DIF entry in FSS-7, thus the methodological quality is "very good," and cross-cultural validity or measurement invariance is "sufficient." The results of the methodological quality and measurement attribute quality assessment of the PSF measurement scale are shown in Tables 2, 3.

3.4 Measurement attribute synthesis results and recommendations

For content validity, FSS-7, FACIT-F, NRS-FRS, and MFI-20 were "not mentioned" and the remaining scales were "uncertain." The construct validity of the MFS was "sufficient," the FSS-7, FACIT-F, and NRS-FRS were "not mentioned," and the remaining scales were "uncertain." The internal consistency of the NRS-FRS was "not mentioned," the FSS and MFS were "sufficient," and the internal consistency of the remaining scales was"uncertain." The hypothesis tests for CIS and FACIT-F were "not mentioned," NRS-FRS "sufficient," and the remaining scales were "uncertain." For stability, FSS-7, CIS, FACIT-F, and MFI-20 are "not mentioned" and the remaining scales are "sufficient." Cross-cultural validity or measurement invariance of the FSS-7 was "full," and the rest of the scales were "not mentioned." Due to the risk of bias, the quality of evidence for the measurement attributes included in this study is mainly "medium" or "low," and the recommendation grade is "B." The synthetic results and recommendations of the PSF measurement scale are shown in Table 4.

4 Discussion

This study included 17 studies involving 10 PSF measurement scales. Although there are many scales available to measure PSF, they

TABLE 2 The evaluation of content validity, structural validity, and internal consistency of PSF measurement scales.

The first author	Scale name	Content validity			Structure validity		Internal consistency	
		Relativity	Comprehensive-ness	Understanding	Index	Evaluation results	Cronbach's α coefficient	Evaluation results
Chun-wei Wu (14)	FSS	D[a]/?	D[a]/?	NR	EFA:1 factor	A/?	0.93	V/+
Nadarajah M et al. (15)	FSS	NR	NR	NR	NR	NR	0.93	D/?
Ozyemisci-Taskiran O et al. (5)	FSS	NR	NR	NR	CFA:1 factor	A/?	0.93	V/+
Abdulla FA et al. (16)	FSS	NR	NR	NR	EFA:1 factor	A/?	0.93	V/+
Lerdal A et al. (17)	FSS-7	NR	NR	NR	NR	NR	0.87	D/?
Chun-wei Wu (14)	FIS	D[a]/?	D[a]/?	NR	EFA:6 factors	A/?	0.92 ~ 0.94	V/+
Saneii S H et al. (6)	FIS	D[a]/?	D[a]/?	A[b]/+	NR	NR	0.87 ~ 0.95	D/?
Batur EB et al. (18)	FIS	NR	NR	NR	NR	NR	0.80 ~ 0.95	D/?
Smith OR et al. (19)	FAS	NR	NR	NR	NR	NR	0.77	D/?
Brândal A et al. (20)	FAS	D[a]/?	D[a]/?	NR	NR	NR	0.82	D/?
Ho LYW et al. (7)	FAS	D[a]/?	D[a]/?	A[b]/+	CFA:2 factors	V/+	0.71 ~ 0.78	V/+
Chen Hongmei et al. (21)	NFI-Stroke	D[a]/?	D[a]/?	D[b]/?	EFA:2 factors	A/?	0.80 ~ 0.91	V/+
Taasen I et al. (22)	NFI-Stroke	D[a]/?	D[a]/?	NR	NR	NR	0.74 ~ 0.89	D/?
Ho LY et al. (23)	NFI-Stroke	D[a]/?	D[a]/?	D[b]/?	CFA and EFA:2 factors CFI = 0.97	V/+	0.69 ~ 0.87	V/−
Chun-wei Wu (14)	CIS	D[a]/?	D[a]/?	NR	EFA:4 factors	A/?	0.76 ~ 0.93	V/+
Butt Z et al. (24)	FACIT-F	NR	NR	NR	NR	NR	0.91	D/?
Chuang LL et al. (25)	NRS-FRS	NR	NR	NR	NR	NR	NR	NR
Liu Xiaoling et al. (26)	MFS	D[a]/?	D[a]/?	D[b]/?	CFA and EFA:4 factors CFI = 0.97	V/+	0.92 ~ 0.96	V/+
Chen Yiting et al. (27)	MFI-20	NR	NR	NR	EFA:6 factors	A/?	0.71 ~ 0.86	V/+

[a]Ask experts.

[b]Ask patients.NR, not reported; CFA, confirmatory factor analysis; EFA, exploratory factor analysis; CFI, comparative fit index; ICC, within-group correlation coefficient; DIF, differential item functioning; +, sufficient; −, inadequate;?, unsure; V, very good; A, adequate; D, doubtful; and I, inadequate.

have different priorities for evaluating PSF, and the quality of their measurement properties is uneven, thus the corresponding test methods also have some problems. In this study, the existing issues in the included scale were analyzed and summarized from both scale validity and reliability, and relevant recommendations combined with the scale dimension were made, aiming to provide some theoretical basis for the selection, verification, or development of PSF-related measurement scales in the future.

Content validity, as the most important measurement attribute of a scale, can directly affect the level of evidence scale. However, most of the included studies did not explicitly mention the evaluation of the content validity of the scale, and only a small number of studies focused on the understanding of the scale. Based on this, in future research involving the development or verify the validity of the scale, in addition to the evaluation of scale validity, the researchers should also try to implement face-to-face interviews with the subjects, so as to intuitively understand the patient's understanding of the scale, and according to the results of the scale content, in order to improve the agreement between the content of the scale and the tested constructs (28). Most of the included studies did not assess the structural validity of the scales. Furthermore, future studies need to present hypotheses between

TABLE 3 The evaluation of hypothesis testing, stability, and cross-cultural validity or measurement invariance of PSF measurement scales.

The first author	Scale name	Hypothesis testing		Stability		Cross-cultural validity or measurement invariance	
		Index	Evaluation results	ICC	Evaluation results	Index	Evaluation results
Chun-wei Wu (14)	FSS	NR	NR	NR	NR	NR	NR
Nadarajah M et al. (15)	FSS	2 comparison scales	V/?	0.93	V/+	NR	NR
Ozyemisci-Taskiran O et al. (5)	FSS	3 comparison scales	V/?	0.74	V/+	NR	NR
Abdulla FA et al. (16)	FSS	3 comparison scales	V/+	0.92	D/+	NR	NR
Lerdal A et al. (17)	FSS-7	2 comparison scales	A/?	NR	NR	DIF	V/+
Chun-wei Wu (14)	FIS	NR	NR	NR	NR	NR	NR
Saneii S H et al. (6)	FIS	2 comparison scales	A/?	0.99	V/+	NR	NR
Batur EB et al. (18)	FIS	3 comparison scales	V/?	0.83	D/+	NR	NR
Smith OR et al. (19)	FAS	NR	NR	NR	NR	NR	NR
Brândal A et al. (20)	FAS	2 comparison scales	V/+	0.73	D/+	NR	NR
Ho LYW et al. (7)	FAS	4 comparison scales	V/?	0.92	D/+	NR	NR
Chen Hongmei et al. (21)	NFI-Stroke	1 comparison scale	V/?	NR	NR	NR	NR
Taasen I et al. (22)	NFI-Stroke	NR	NR	NR	NR	NR	NR
Ho LY et al. (23)	NFI-Stroke	4 comparison scales	V/?	0.93	D/+	NR	NR
Chun-wei Wu (14)	CIS	NR	NR	NR	NR	NR	NR
Butt Z et al. (24)	FACIT-F	NR	NR	NR	NR	NR	NR
Chuang LL et al. (25)	NRS-FRS	1 comparison scale	V/+	0.95	V/+	NR	NR
Liu Xiaoling et al. (26)	MFS	1 comparison scale	V/?	0.85	V/+	NR	NR
Chen Yiting et al. (27)	MFI-20	1 comparison scale	V/?	NR	NR	NR	NR

Same as "note" at the bottom of Table 2.

comparative scales before hypothesis testing; cross-cultural validity or measurement invariance should be evaluated. The scale reliability involved in this study included internal consistency and stability. It should be noted that when evaluating the internal consistency of multidimensional scales, the Cronbach's α coefficient of the total scale and each subscale should be calculated simultaneously to clarify the reliability of each dimension of the scale. The stability of the scales included in this study was responded to by test–retest reliability. At present, researchers choose the retest time based on the hospitalization time of patients or from their own experience. There is no unified standard, which will affect the retest reliability of the scale to some extent. Therefore, future relevant studies should not only clarify the time interval between the two measurements but also clarify the basis for the selection of the retest time.

None of the scales included in this study evaluated responsiveness, measurement error, and criterion validity. Because the causal mechanism and specific features of PSF are still largely unknown (29), there is no golden standard for measuring PSF, thus it is impossible to evaluate the validity of PSF-related measurement scales. The FSS-7 included in this study was obtained after deleting two entries from the original FSS, but the study did not compare it with the original FSS to evaluate standard validity. Although Lenaert et al. (30) highlighted that there was a weak to moderate and strong correlation between the fatigue experience of patients with PSF and the FSS and FSS-7 scales, it also did not mention the content related to validity. Based on this, when the new scale is developed based on the original scale in the future, the new scale can be compared with the original scale, so as to complete the evaluation of the validity standard.

This study showed that FSS was the most evaluated scale, followed by FIS, FAS, and NFI-stroke, and none of these scales were evaluated for cross-cultural validity or measurement invariance. Although FSS-7 evaluated cross-cultural validity or measurement invariance, only one included study evaluated CIS, FACIT-F, NRS-FRS, MFS, and MFI-20, and more studies are needed to test whether the above scale is clinically applicable in the future. FSS has 9 items, and the evidence quality level of content validity and internal consistency corresponds to "medium" and "high," respectively, which are also widely used in clinical practice. This is consistent with the findings of Kjeverud et al. (8). More research is needed in the future to clarify and harmonize the measurement tools for PSF. Therefore, this study temporarily recommends FSS for PSF measurement, but more tests still need to be conducted on its relevant measurement attributes, especially the cross-cultural validity or measurement invariance. In addition, the FSS is a unidimensional scale that can only assess somatic fatigue. For a multidimensional PSF assessment, perhaps FIS, FAS, and NFI-stroke should be considered. However, the above measurement scale should also be tested with more relevant measurement properties to verify its clinical applicability. This study also has some limitations as follows: ① only Chinese and English literature are included, there may be language bias; ② PSF scale has only one study included in the evaluation, which may affect the results of this study to some extent; ③ some scales have

TABLE 4 The synthetic results and recommendations of the PSF measurement scale.

Scale name	Content validity		Structure validity		Internal consistency		Hypothesis test		Stability		Cross-cultural validity or measurement invariance		Recommended grade
	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	Overall rating	Quality of evidence	
FSS	?	Middle	?	Middle	+	High	?	Middle	+	Middle	NR	NR	B
FSS-7	NR	NR	NR	NR	?	Middle	?	Middle	NR	NR	+	High	B
FIS	?	Middle	?	Low	?	Middle	?	Middle	+	Middle	NR	NR	B
FAS	?	Middle	?	Middle	?	Middle	?	High	+	Middle	NR	NR	B
NFI-Stroke	?	Middle	?	Middle	?	Middle	?	Middle	+	Middle	NR	NR	B
CIS	?	Middle	?	Low	?	Middle	NR	NR	NR	NR	NR	NR	B
FACIT-F	NR	NR	NR	NR	?	Low	NR	NR	NR	NR	NR	NR	B
NRS-FRS	NR	NR	NR	NR	NR	NR	+	Middle	+	Middle	NR	NR	B
MFS	?	Middle	+	High	+	High	?	Middle	+	Middle	NR	NR	B
MFI-20	NR	NR	?	Low	?	Middle	?	Middle	NR	NR	NR	NR	B

+, sufficient; −, inadequate;?, unsure; and NR, not mentioned.

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not been studied with large samples, thus the results of this study need to be interpreted carefully.

5 Conclusion

In summary, this study temporarily recommended FSS to measure PSF. To assess the PSF more comprehensively, the use of FIS, FAS, and NFI-stroke should be considered. All 10 PSF measurement scales involved in this study need to be studied to verify their validity. In future, when selecting, validating, or developing PSF-related measurement scales, the relevant assessment problems of the inclusion scales mentioned in this study should be avoided as far as possible, in order to get more high-quality evidence support and more scientific and standardized measurement tools.

Author contributions

LW: Methodology, Software, Writing – original draft, Writing – review & editing. HJ: Data curation, Software, Writing – review & editing.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy and safety of very early rehabilitation for acute ischemic stroke: a systematic review and meta-analysis

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Background: Early rehabilitation after acute ischemic stroke (AIS) contributes to functional recovery. However, the optimal time for starting rehabilitation remains a topic of ongoing investigation. This article aims to shed light on the safety and efficacy of very early rehabilitation (VER) initiated within 48h of stroke onset.

Methods: A systematic search in PubMed, Embase, Cochrane Library, and Web of Science databases was conducted from inception to January 20, 2024. Relevant literature on VER in patients with AIS was reviewed and the data related to favorable and adverse clinical outcomes were collected for meta-analysis. Subgroup analysis was conducted at different time points, namely at discharge and at three and 12 months. Statistical analyses were performed with the help of the Meta Package in STATA Version 15.0.

Results: A total of 14 randomized controlled trial (RCT) studies and 3,039 participants were included in the analysis. VER demonstrated a significant association with mortality [risk ratio (RR) = 1.27, 95% confidence interval (CI) (1.00, 1.61)], ability of daily living [weighted mean difference (WMD) = 6.90, 95% CI (0.22, 13.57)], and limb motor function [WMD = 5.02, 95% CI (1.63, 8.40)]. However, no significant difference was observed between the VER group and the control group in adverse events [RR = 0.89, 95% CI (0.79, 1.01)], severity of stroke [WMD = 0.52, 95% CI (−0.04, 1.08)], degree of disability [RR = 1.06, 95% CI (0.93, 1.20)], or recovery of walking [RR = 0.98, 95% CI (0.94, 1.03)] after stroke. Subgroup analysis revealed that VER reduced the risk of adverse events in the late stage (at three and 12 months) [RR = 0.86, 95% CI (0.74, 0.99)] and degree of disability at 12 months [RR = 1.28, 95% CI (1.03, 1.60)], and improved daily living ability at 3 months [WMD = 4.26, 95% CI (0.17, 8.35)], while increasing severity of stroke during hospitalization [WMD = 0.81, 95% CI (0.01, 1.61)].

Conclusion: VER improves activities of daily living (ADLs) and lowers the incidence of long-term complications in stroke survivors. However, premature or overly intense rehabilitation may increase mortality in patients with AIS during the acute phase. PROSPERO registration number: CRD42024508180.

Systematic review registration: This systematic review was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/). PROSPERO registration number: CRD42024508180.

KEYWORDS

rehabilitation, early ambulation, ischemic stroke, prognosis, meta-analysis

1 Introduction

Acute ischemic stroke (AIS) refers to the abrupt onset of focal neurological dysfunction resulting from insufficient blood supply to the brain or determined according to objective evidence of vascular origin observed through imaging or pathological examination (1). It features high incidence, recurrence, disability, and mortality worldwide (2), and represents approximately 80% of all stroke cases (3). In the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification system, large-artery atherosclerosis and cardioembolism are the main etiologies of stroke, with contributing risk factors including cardiovascular, endocrine, and others. Stroke, as the second leading cause of death and disability worldwide according to the Global Burden of Disease Study in 2016 (4), imposes substantial health and economic burdens in both developed and developing nations. Moreover, there has been a gradual increase in stroke incidence among young populations (5, 6). The progression of ischemic stroke is commonly categorized into acute, subacute, and chronic phases; however, the temporal boundaries of these stages are inconsistently defined. In the present study, acute stroke was defined as a stroke that occurs within 7 days after the onset, subacute stroke was a stroke occurring more than 7 days and less than 3 months after the onset, and chronic stroke generally referred to a non-recurrent stroke that lasts 3 months. Despite advancements in stroke unit management and early revascularization which promote timely recovery of brain blood flow in recent years, 50% of patients became chronically disabled with low life quality (7), because neural restoration was constrained by a narrow therapeutic window and irreversible damage to neuron. Some stroke survivors experience lingering complications and sequelae, particularly motor impairment and cognitive decline (8). In a recent study, it was demonstrated that acute or subacute stroke patients with *Clostridium difficile* infection exhibited significant improvement in basic living ability at discharge after 3 h of daily neurorehabilitation, but no significant difference was found in comparison to non-infected patients (9). Therefore, in addition to standard care, systematic, regular and intensive rehabilitation is of great importance in the early period of stroke even in the presence of other complications such as infections, unless patients have malaise or worse symptoms.

Post-stroke rehabilitation, as a long and relatively safe intervention, is conducive to restoring limb motivation, improving walking and balancing abilities, and reducing the incidence of disability, falls and cardiorespiratory diseases (10). Initiating rehabilitation promptly after the stabilization of vital signs would help to accelerate the recovery of central nervous system and prevent potential complications (11). Sun et al. suggested that early rehabilitation could influence the expression of serum inflammatory factors, such as vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), interleukin-10, and stromal cell-derived factor-1α, and motivate endothelial progenitor cells (12), thereby promoting endothelial formation and vascular regeneration in AIS (13). However, the optimal timing for commencing early rehabilitation after stroke remains controversial, with uncertainty regarding the safety and efficacy of very early rehabilitation (VER) in patients with AIS. Firstly, for patients with post-stroke paralysis, very early out-of-bed activities may precipitate falls due to weak limb strength or poor balancing ability. Moreover, significant head position change after stroke would decrease cerebral blood flow (14), which could aggravate ischemia in the infarct area and lead to deterioration of the disease, while maintaining a supine position could increase cerebral perfusion pressure and boost collateral circulation to support the ischemic penumbra (15, 16). Despite the absence of definitive evidence and a lack of consensus regarding the optimal rehabilitation strategy, which involves starting time, frequency and intensity (17, 18), VER has been advocated within some published stroke guidelines (19, 20), and merits further exploration. Notably, a recent meta-analysis of randomized controlled trials (RCTs) conducted in 2021 revealed positive efficacy of early rehabilitation at 3 months. No statistical difference in adverse events and disability rate was noted between the VER group and control group, but the study did not assess outcomes in different endpoints (21).

This meta-analysis included RCTs to evaluate the effects of initiating VER within 48 h of stroke onset on short- and long-term recovery. Additionally, a subgroup analysis at different time points (at discharge, 3 months and 12 months) was performed to observe the dynamic changes of the efficacy and safety of VER, which could serve as a reference for clinical practice.

2 Methods

This systematic review was conducted and reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (22), and registered with PROSPERO (CRD42024508180).

2.1 Search strategy

Two investigators independently searched PubMed, Embase, Web of Science, and the Cochrane Library from inception until January 20, 2024. Medical Subject Headings (MeSH) terms and free-text words, including "ischemic stroke" and "early ambulation or early mobilization or rehabilitation" and "early," were employed in the search process. Other relevant literature was acquired based on the reference list of included studies. The search terms and strategies are detailed in Supplementary material 1.

2.2 Inclusion and exclusion criteria

The inclusion criteria of the meta-analysis were as follows: (1) Population: Patients aged 18 or older who met the diagnostic criteria for AIS and were admitted to the hospital within 48 h of the onset were included; (2) Intervention: VER was initiated within 48 h of stroke onset in the experiment group; (3) Control: The control group received either standard care or delayed rehabilitation; (4) Outcomes: The main outcomes included indicators of safety, severity and function. Safety and severity indicators included: (1) Mortality: It was defined as the proportion of death or modified Ranking Score (mRS) rated as 6. The mRS was an ordinal scale ranging from 0 (no disability) to 5 (severe disability), with a score of 6 indicating decease (23). (2) Adverse events: It was defined as the proportion of non-fatal adverse events after stroke, including immobility-related and neurological complications after the attack. (3) National Institutes of Health Stroke Scale (NIHSS): It was the most widely employed measure of stroke severity to evaluate the

efficacy of treatment strategies for AIS (24). Indicators of physical function encompassed: (1) mRS: It was a favorable outcome defined as mRS of 0–2 (no or minimum disability), and the proportion of mRS of 0–2 was used to assess the improvement of disability. (2) Barthel Index (BI): It was a valid 10-item tool used to assess patient independence for ADLs in stroke (25). There were two kinds of scales, with a total of score of 0–100 and 0–20, respectively (26, 27). The two scales had consistent content and clinimetrics. The total score summed to 20 or 100, with higher scores indicating better performance (26). Among the eligible studies, Cumming and Langhorne applied the 0–20 scale, while the others employed the 0–100 scale. (3) Fugl-Meyer assessment (FMA): FMA consisted of two subscales to assess upper and lower extremities motor function. Higher scores mean better limb mobility (28). (4) The proportion of walking 50 m unassisted: It referred to the proportion of patients walking over 50 m by 3 months without assistance and was adopted to estimate independent walking ability. (5) Study design: All studies were RCTs and published in English. Studies were excluded if the full text was not accessible, the details regarding intervention was unclear, the intervention did not meet the criteria, or relevant outcome indicators were absent. Besides, reviews, meta-analyses, case reports, conference abstracts, incomplete clinical protocols, animal experiments and duplicate publications were also removed.

2.3 Data extraction

Two researchers independently screened the literature based on the inclusion and exclusion criteria, extracted important information from every eligible study, and developed standardized tables. The extracted data included the following variables: the first author, publication year, country, sample size, average age, sex ratio, intervention of each group, the start time of early rehabilitation in the VER group and outcome measures. Discrepancies were resolved through discussion or consultation with another author to achieve consensus.

2.4 Quality assessment of included studies

The quality of included studies was assessed using the Cochrane Collaboration's tool. The assessment for possible bias identification included seven items: generation of randomized sequences, allocation concealment blinding of implementers and participants, blinding of outcome assessors, completeness of outcome data, selective reporting of study results, and other potential sources of bias (29, 30). The studies were classified as having low, unclear, or high risk of bias. Those meeting all criteria were categorized as having a "low risk," which indicated high quality and minimal overall bias. Those partially meeting the criteria were classified as having an "unclear risk," which suggested moderate potential for bias. Those failing to meet the criteria were labeled as having a "high risk," which reflected a notable risk of bias and lower quality. Consensus was reached on any discrepancies or disagreements.

2.5 Statistical analysis

Stata 15.0 software was used to perform statistical analysis of the collected data. Weighted mean difference (WMD) and 95% confidence interval (CI) were utilized to describe continuous variables, and relative risk (RR) and 95% CI were used for dichotomous variables. Different statistical models were chosen according to the presence of heterogeneity, which was assessed by I^2 values or Cochran's Q-statistics. Values of $I^2 < 25\%$, ≥ 25 to $<50\%$, ≥ 50 to $<75\%$, and $\geq 75\%$ indicated none, low, moderate, and high heterogeneity, respectively. Heterogeneity was considered significant when $p < 0.05$ and $I^2 > 50\%$. The data were analyzed through a fixed-effects model when the I^2 value was less than 50% ($p > 0.05$, $I^2 < 50\%$). Instead, if the I^2 value was equal to or greater than 50% ($p < 0.05$, $I^2 \geq 50\%$), a sensitivity analysis was conducted to explore potential sources of heterogeneity, and statistical analysis was performed with a fixed-effects model. In addition, publication bias was evaluated via a funnel plot and was quantified through Egger tests. Finally, subgroup analysis by time was conducted to further understand the effects of the intervention on outcomes such as adverse events, mRS, BI, and NIHSS in both short and long terms.

3 Results

3.1 Study selection

The literature search and selection process is presented in Figure 1. A total of 9,643 studies were initially identified for screening. After the removal of 3,294 duplicate articles and 6,323 articles that did not meet the predefined inclusion criteria, the full texts of 26 RCTs were reviewed. Following this full-text assessment, two studies were excluded due to insufficient data for statistical analysis. Further scrutiny revealed that 10 were ineligible because they either initiated VER on the experiment group after 48 h, commenced rehabilitation on the control group after 24 h but within 48 h, or lacked specification regarding the timing of interventions. At last, a total of 14 studies met the eligibility criteria and were finally included for subsequent analysis. Among them, Van Wijk et al. and Cumming et al. reported extended outcomes of the same study population in the research by Bernhardt et al. in 2007. Bernhardt et al. provided additional results in a study published in 2021 to complement the 2015 research.

3.2 Characteristics of trials and risks of bias

The characteristics of 14 eligible RCTs are detailed in Table 1. The total sample size comprised 3,039 participants, with 1,544 in the experiment group and 1,495 in the control group. The study populations were from diverse geographic regions: four studies originated from China (31–34), five from Australia (35–39), one from India (40) and four from Europe (41–44). Regarding the time of initiating rehabilitation, VER was started within 24 h after stroke in 10 studies (17, 35–37, 39–44), between 24 and 48 h in two studies (32, 33) and within 48 h in two studies (31, 34). The risks of bias are shown in Figures 2, 3.

3.3 Meta-analysis results

3.3.1 Mortality

In six studies (17, 34, 35, 39, 41, 43), mortality was assessed at varying intervals following stroke onset: five studies at 3 months, one

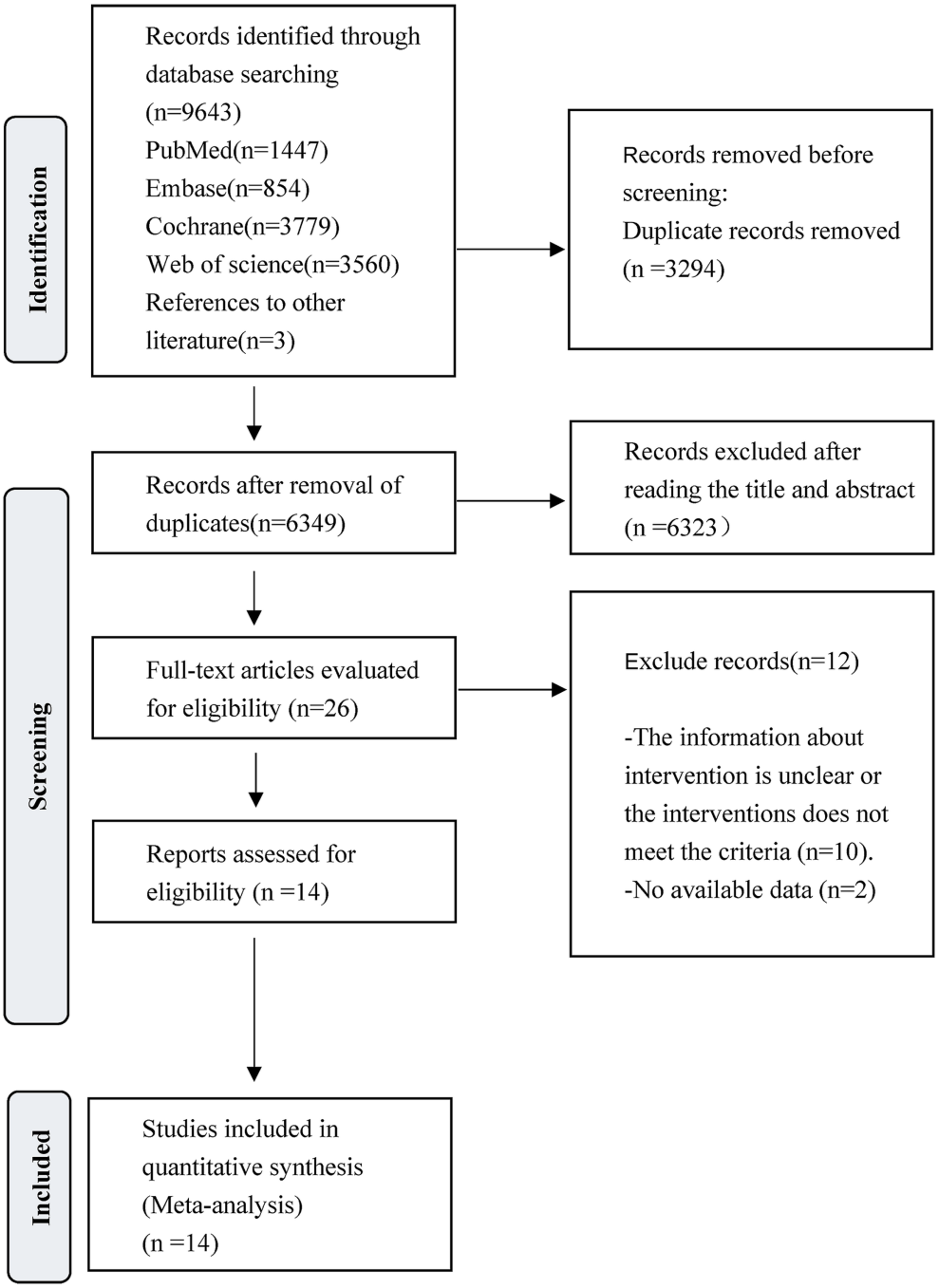

FIGURE 1
PRISMA flow diagram of the study process. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

at 14 days, and one at 12 months. Unless otherwise specified, all figures represent assessments at 3 months after the onset. Given the absence of heterogeneity (I^2 = 0.0%, p = 0.562), a fixed-effects model was employed to analyze the mortality data. The results of the meta-analysis (Figure 4) suggested that VER would raise the risk of death in stroke patients [RR = 1.27, 95% CI (1.00, 1.61)].

3.3.2 Adverse events and its subgroup analysis

Seven articles (34, 35, 37, 39, 41–43) involved the non-fatal adverse events. In view of the low heterogeneity (I^2 = 33.1%, p = 0.164), a fixed-effects model was used. The results of the analysis (Figure 5A) demonstrated no significant difference in incidence of adverse events between the VER group and the control group [RR = 0.89, 95% CI (0.79, 1.01)]. Two of these studies evaluated the incidence of complications at 14 days after stroke or during hospitalization, in the early stage of stroke recovery, while the remaining five focused on the recovery period after stroke (at 3 months or 12 months), reflecting a relatively long-term outcome. Subgroup analysis (Figure 5B) based on time was performed to dynamically observe the short-term or long-term effects of VER. VER could decrease the risk of adverse events

TABLE 1 Characteristics of trials.

Study	Year	Country	Sample size		Gender (M/F)	Mean age (years)		Intervention		Start-up time of EG	Outcome (Assessment time)
			EG	CG		EG	CG	EG	CG		
Bernhardt	2007	Australia	38	33	38/33	74.6	74.9	VER (very early out-of-bed activities) + SC	SC	≤24 h	F5 (at 3 months); F7 (at 3 months; at 12 months)
Langhorne	2010	U.K.	16	16	16/16	63	71	VER (very early out-of-bed activities) + SC	SC	≤24 h	F3; F5; F6; F7 (at 3 months)
Van Wijk (Further results of Bernhardt 2007)	2011	Australia	38	33	38/33	74.6	74.9	VER (very early out-of-bed activities) + SC	SC	≤24 h	F6 (at 3 months)
Cumming (Further results of Bernhardt 2007)	2012	Australia	38	33	38/33	74.6	74.9	VER (very early out-of-bed activities) + SC	SC	≤24 h	F3 (at 3 months; at 12 months)
Bernhardt	2015	Australia	1,054	1,050	1,286/818	72.3	72.7	VER (very early out-of-bed activities) + SC	SC	≤24 h	F2; F5; F6; F7 (at 3 months)
Chippala	2015	India	40	40	42/38	59.32	60.57	VER (very early out-of-bed activities) + SC	SC	≤24 h	F3 (at 3 months)
Herisson	2016	France	63	75	89/49	68.1	71.2	Very early sitting + SC	Progressive sitting at different angles in the first few days + SC Day0 at 30° Day1 at 45° Day2 at 60°	≤24 h	F3 (at 3 months); F4 (at discharge; at 3 months); F5 (at 3 months); F6 (during hospitalization); F7 (at discharge; at 3 months)
Morreale	2016	Italy	110	60	122/48	64	63	VER (very early out-of-bed activities) + SC	DR (intensive rehabilitation from the 5th day)	≤24 h	F3 (at 3 months; at 12 months); F6 (at 3 months)
Zhang	2019	China	48	48	57/39	Age group ≥40, 21 <40, 27	≥40, 20 <40, 28	VER (limb movement)	SC	24–48 h	F1 (unmentioned)
Wu	2020	China	16	15	22/9	61.06	62.67	VER (lower limb exercise strengthening)	SC	≤24–48 h	F2; F7 (at 3 months)
Bernhardt (Further result of Bernhardt 2015)	2021	Australia	1,054	1,050	1,286/818	72.3	72.7	VER (very early out-of-bed activities) + SC	SC	≤24 h	F5; F6 (at 14 days)

(Continued)

TABLE 1 (Continued)

Study	Year	Country	Sample size		Gender (M/F)	Mean age (years)		Intervention		Start-up time of EG	Outcome (Assessment time)
			EG	CG		EG	CG	EG	CG		
Fudong Wang	2022	China	56	54	65/45	60.27	61.04	VER (limb movement in or out of bed) + SC	DR (within 72–96 h) + SC	24–48 h	F1; F7 (at 3 months)
Wei Wang	2022	China	52	51	82/21	58	62	VER (very early out-of-bed activities) + Routine rehabilitation	Routine rehabilitation (≥48 h)	≤48 h	F3; F5; F6; F7 (at 3 months; at 12 months)
Anjos	2023	Germany	51	53	55/49	61.80	58.89	VER (very early out-of-bed activities)	SC	≤12 h	F4; F7 (at discharge; at 3 months)

M, male; F, female; EG, Experimental Group; CG, Control Group; VER, Very early rehabilitation; SC, standard cure; DR, delayed rehabilitation; F1, FMA, Fugl-Meyer Assessment, measuring motor impairment; F2: Proportion of walking 50m unassisted; F3, BI, Barthel Index; F4, NIHSS, the National Institutes of Health Stroke Scale; F5, death/mortality; F6, the proportion of post-stroke adverse events; F7, mRS, modified Rankin Scale.

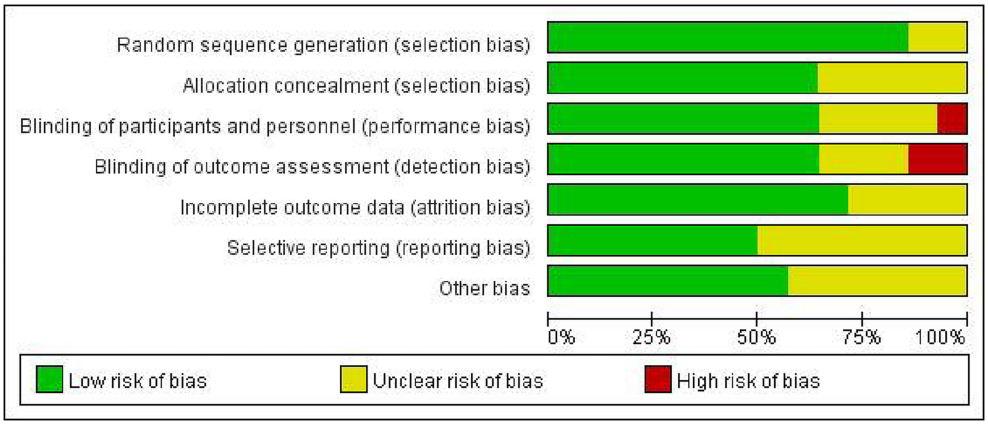

FIGURE 2
Graph for risk of bias.

assessed at three and 12 months [RR = 0.86, 95% CI (0.74, 0.99)], but could not significantly lower the risk in the early stage [RR = 0.99, 95% CI (0.79, 1.24)].

3.3.3 Severity of stroke: NIHSS and its subgroup analysis

Two studies (41, 44) reported the outcomes of NIHSS at discharge or at 3 months. The heterogeneity was not significant (I^2 = 0.0%, p = 0.535). The fixed-effects model was applied (Figure 6A), and the analysis results revealed no significance in stroke severity between the two groups [WMD = 0.52, 95% CI (−0.04, 1.08)]. In the subgroup analysis (Figure 6B), there was a slight difference in NHISS assessed at discharge between the two groups [WMD = 0.81, 95% CI (0.01, 1.61)] but no significant difference was observed at 3 months [WMD = 0.25, 95% CI (−0.53, 1.02)].

3.3.4 Degree of disability: mRS and its subgroup analysis

Eight studies (17, 31, 33–35, 41, 43, 44) reported on mRS, with eight assessed at 3 months after the onset of stroke, two at 12 months and two at discharge. Given significant heterogeneity (I^2 = 52.9%, p = 0.016), a random-effects model was utilized to analyze the mRS data, but no significant difference was noted [RR = 1.06, 95% CI (0.93, 1.20)] (Figure 7A). The sensitivity analysis showed a low sensitivity and stable results for this outcome (Supplementary Figure 1). Subgroup analysis indicated that the risk of serious disability in the VER group was lower than that in the control group [RR = 1.28, 95% CI (1.03, 1.60)] at 12 months, while there was no significant reduction in the risk of disability measured at discharge [RR = 0.86, 95% CI (0.71, 1.05)] and at 3 months after stroke [RR = 1.08, 95% CI (0.92, 1.27)] (Figure 7B).

3.3.5 Daily activity ability: BI and its subgroup analysis

Six articles (34, 36, 40–43) reported on BI in post-stroke patients. The studies were heterogeneous (I^2 = 93.4%, p = 0.000). Meta-analysis was carried out with the random effects model, and the results suggested that VER could improve the BI of stroke patients [WMD = 6.90, 95% CI (0.22, 13.57)] (Figure 8A). None of these studies were found to influence the aggregated estimates in the

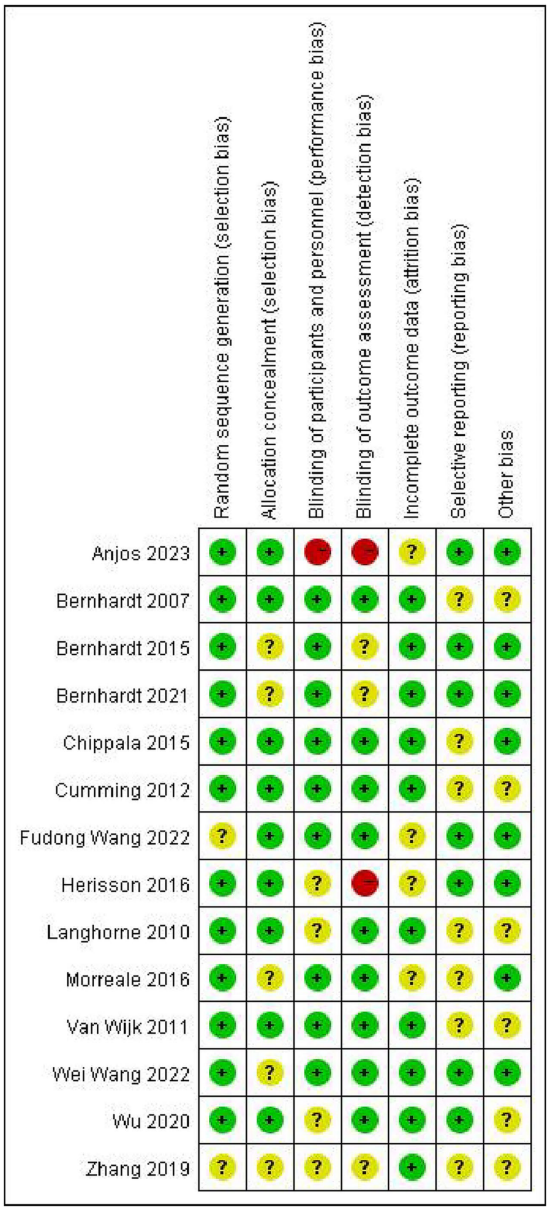

FIGURE 3
Summary for risk of bias.

sensitivity analysis (Supplementary Figure 2). In subgroup analysis, the improvement in BI remained significant at 3 months [WMD = 4.26, 95% CI (0.17, 8.35)], while no significant effect of VER on BI was noted at 12 months after stroke [WMD = 9.52, 95% CI (−3.02, 22.06)] (Figure 8B).

3.3.6 Limb motor function: FMA

Two articles (32, 33) focused on FMA scores in patients after treatment. One assessed the overall FMA, and the other reported FMA scores for the upper and lower limbs separately. Moderate heterogeneity was noted ($I^2 = 71.6\%$, $p = 0.030$), and sensitivity analysis indicated low sensitivity (Supplementary Figure 3). The results of the random effects model indicated that VER contributed to the restoration of motor mobility [WMD = 5.02, 95% CI (1.63, 8.40)] (Figure 9).

3.3.7 Proportion of walking 50 m unassisted

Two (31, 35) articles investigated the proportion of walking 50 m unassisted in patients at 3 months after stroke. The studies exhibited no heterogeneity ($I^2 = 0.0\%$, $p = 0.546$), and the fixed-effects model was used for meta-analysis [RR = 0.98, 95% CI (0.94, 1.03)], which demonstrated that VER cannot expedite the recovery of the ability to walk independently within 3 months (Figure 10).

3.3.8 Publication bias

Publication bias was detected through funnel plots and Egger's test for change in mortality, adverse events, NIHSS, mRS, BI, and FMA. Results indicated potential publication bias for mRS ($p = 0.035$) and no publication bias for mortality ($p = 0.204$), adverse events ($p = 0.052$), NIHSS ($p = 0.174$), BI ($p = 0.558$), and FMA ($p = 0.947$) (Supplementary Figures 4–9).

4 Discussion

This meta-analysis proved that VER could elevate the risk of death after stroke and stroke severity during hospitalization. However, it significantly lowered the risk of long-term complications or disability and had positive effects on improving daily living abilities and limb movement recovery after stroke.

Since the Swedish Consensus Conference on Stroke Care in the mid-1980s, VER, which comprises out-of-bed sitting, standing, and walking, has been recognized as an important part of unit care for acute stroke and incorporated into national guidelines around 1994 (45–47). Despite growing attention from guidelines and expert consensus on early rehabilitation, agreement was not reached regarding when (appropriate start time and duration) and how (intervention type, intensity, frequency, amount) to perform VER. Therefore, the safety and efficacy of VER in acute stroke patients remains a concern for clinicians.

A Cochrane review revealed a trend toward increased mortality at 3 months in the most relevant trials, although the difference was not significant between VER and delayed or lower-dose mobilization (11). Sundseth et al. noted a higher proportion of deaths at 3 months in the VER group mobilized within 24 h of admission in comparison to the control group mobilized between 24 and 48 h, but the difference was not significant though stroke severity was adjusted (48). The result of our meta-analysis showed that VER raised the risk of death in patients [RR = 1.27, 95% CI (1.00, 1.61)]. An important distinction between this study and others was the variation in assessment times. Among the eligible studies, one study considered 14-day mortality while others focused on mortality over 3 months. It is essential to exercise caution in concluding that VER-related mortality was more likely to occur shortly after stroke, as only one study has examined the 14-day mortality. Nonetheless, given the large sample size from the study included in the analysis, we cannot disregard that the observed 27% mortality rate may cause fatal harm to AIS population receiving VER treatment. Notably, the study indicated that patients aged over 80 or those with intracranial hemorrhage exhibited a higher mortality rate (39). During the progression of AIS, although the majority of patients experience gradual recovery, a significant number of patients have not substantially recovered or their conditions even deteriorated during the subsequent 24–72 h (49). This period was marked by considerable clinical uncertainty (45). Stroke-related events, including stroke

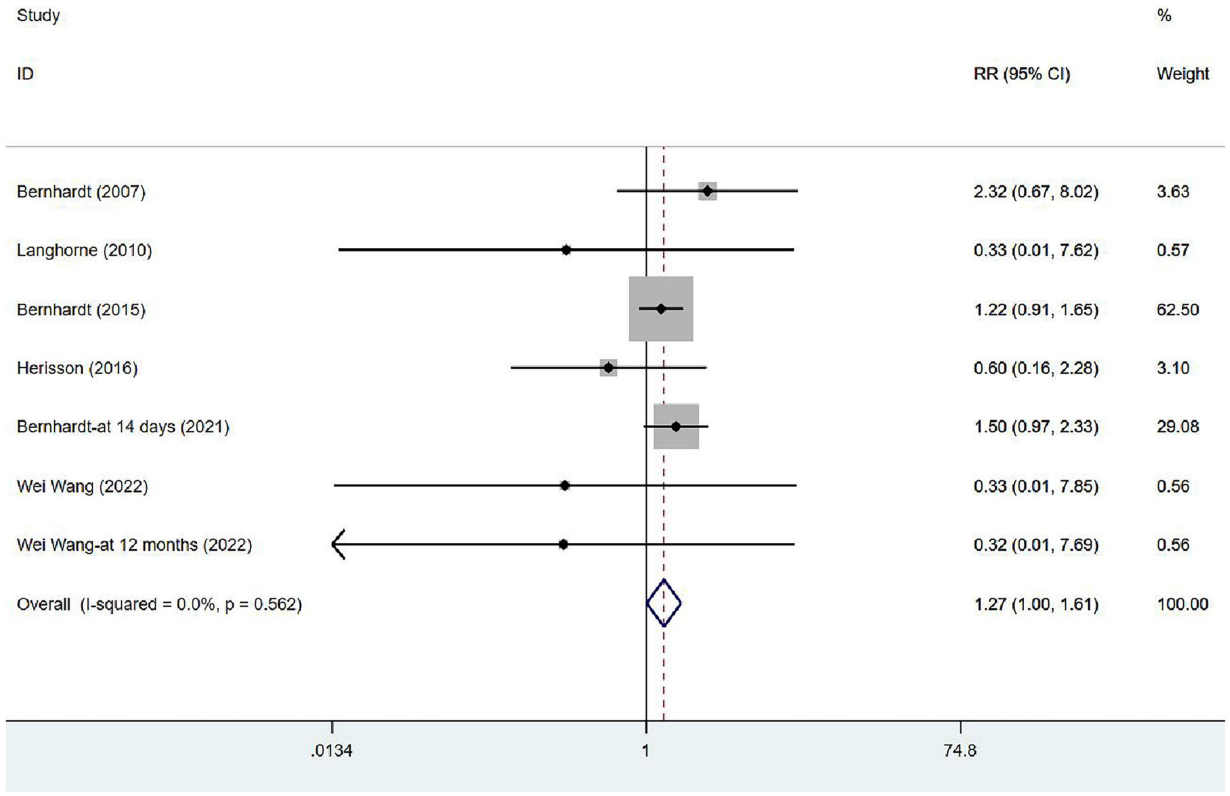

FIGURE 4
Forest plot of meta-analysis of mortality. Comparison: the effect of VER on the mortality rate after stroke. Statistical method: Inverse-variance of the fixed effects model [relative risk (RR) and 95% confidence interval (CI)]. very early rehabilitation (VER).

progression or recurrence, are the most common causes of death within 14 days (39), and likely attributed to early neurological deterioration predominantly arising from intracranial hemorrhage and vasogenic edema (50, 51). The subgroup analysis of NIHSS in the present analysis revealed a statistically significant difference in NIHSS assessed at discharge between the two groups [WMD = 0.81, 95% CI (0.01, 1.61)], but no difference was observed at 3 months. This finding may offer insight into the elevated mortality noted in the VER group. Early neurological deterioration within 24 h of AIS was associated with increased mortality (50), which may be helpful for identifying predictors of death in patients undergoing early rehabilitation. Proximal arterial occlusion (52, 53), failure of recanalization and insufficient cerebral hemodynamic reserve (54) found through imaging were demonstrated to be correlated with deterioration. Moreover, severe white matter hyperintensities might be linked to poor prognosis after AIS due to impaired brain microcirculation (55). Elevated adrenomedullin has been considered as an independent predictor of AIS outcomes in recent years (56) and a novel plasma biomarker related to the increased mortality in AIS patients undergoing early rehabilitation (57), possibly due to the involvement of adrenomedullin receptor genes in vascular injury (58). Therefore, both image and plasma prediction tools can help clinicians identify VER patients at a high risk of death.

Premature out-of-bed movement and head position change within 24 or 48 h may induce unpredictable alterations in both intracranial and systemic hemodynamics (14, 59), and accelerate the deterioration, especially after 48 h of the onset of symptoms when the infarction edema reached its peak, which necessitates restricted head positioning (16). There were conflicting reports regarding the outcomes of AIS patients receiving thrombolytic therapy. Alteplase thrombolysis was expected to cause dropped embolus and a new embolic event, and induce hemorrhagic transformation, but the incidence of neurological deterioration in patients who did not have thrombolytic therapy was higher than those receiving thrombolysis (50). One study suggested that early rehabilitation reduced the risk of death within 3 months in patients with large artery occlusive stroke receiving endovascular treatment (60), whereas another small-scale study, which did not address endovascular therapy, reported increased mortality in patients who underwent early upright exercise. In addition to reconstructing brain circulation, adaptation to the state of ischemia or hypoxia to activate angiogenesis and neuroprotection is also a complementary strategy for early rehabilitation to avoid adverse outcomes. Intermittent hypercapnic hypoxia, which contributed to neuroprotection (61), could be applied in rehabilitation in stroke treatment, but current studies have not evaluated its impact on the mortality (62). Tong et al. investigated the safety of remote ischemic conditioning followed by exercise in the Phase 1 clinical trial and no significant difference was found in a small number of samples (63). Wang et al. demonstrated in a rat model that exercise following remote ischemic conditioning led to elevated expression of mRNA and proteins associated with neuroplasticity and angiogenesis (64). These studies explore a novel and comprehensive rehabilitation strategy, and larger clinical trials are needed in the future.

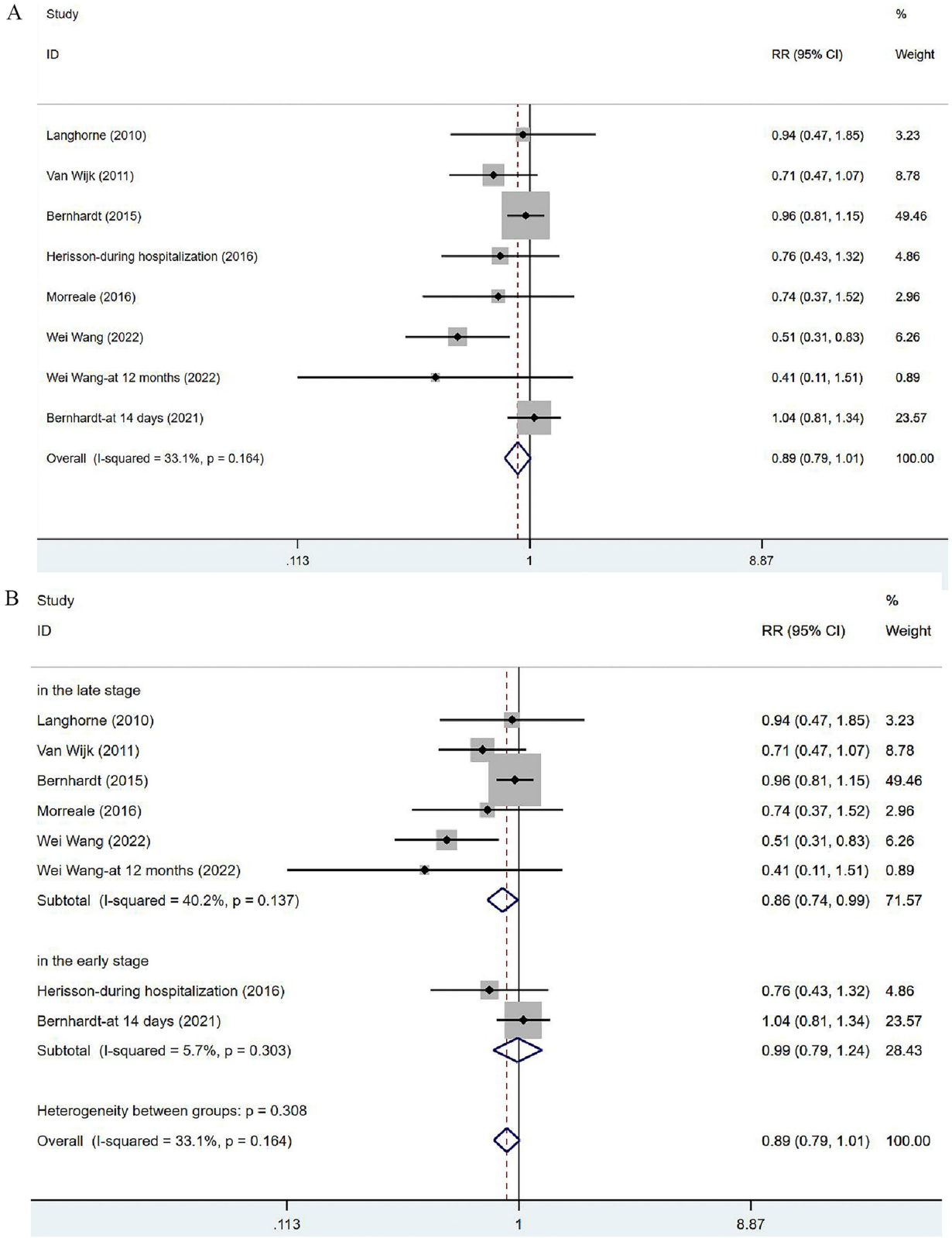

FIGURE 5
Forest plot of the adverse events. (A) Forest maps of meta-analysis of adverse events. (B) Forest maps of subgroup analysis of adverse events. (A) Comparison: the effect of VER on the proportion of adverse events after stroke. Statistical method: Inverse-variance of the fixed effects model [relative risk (RR) and 95% confidence interval (CI)]. Very early rehabilitation (VER). (B) Comparison: the effect of VER on the proportion of adverse events after stroke at different endpoints. Very early rehabilitation (VER); RR, risk ration; 95% CI, 95% confidence interval.

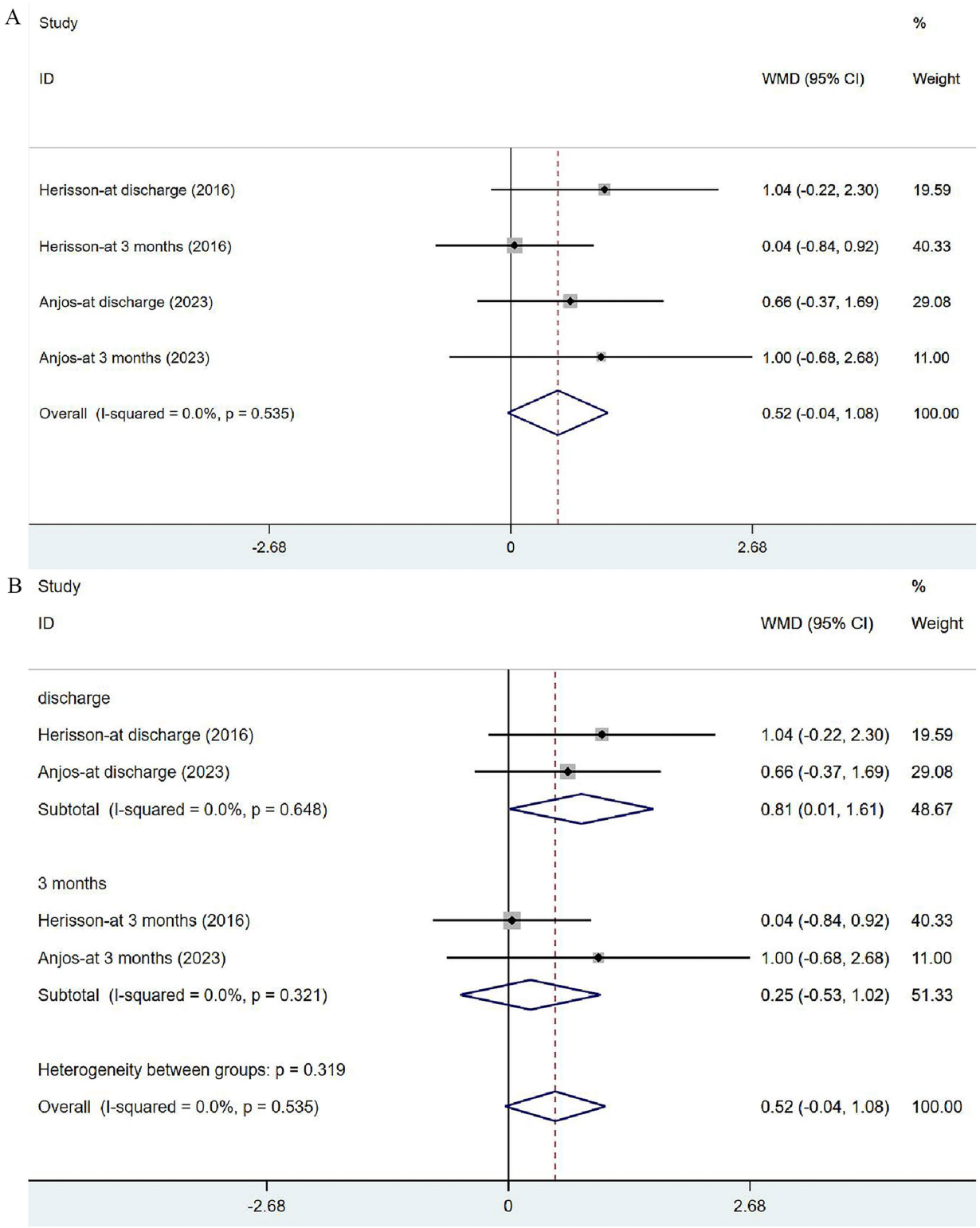

FIGURE 6
Forest plot of the NIHSS. (A) Forest maps of meta-analysis of NIHSS. (B) Forest maps of subgroup analysis of NIHSS. (A) Comparison: the effect of VER on NHISS. Statistical method: Inverse-variance of the fixed effects model [weighted mean difference (WMD) and 95% confidence interval (CI)]. National Institutes of Health Stroke Scale (NIHSS); very early rehabilitation (VER). (B) Comparison: the effect of VER on NIHSS after stroke at different endpoints. National Institutes of Health Stroke Scale (NIHSS); very early rehabilitation (VER); weighted mean difference (WMD); 95% CI: 95% confidence interval.

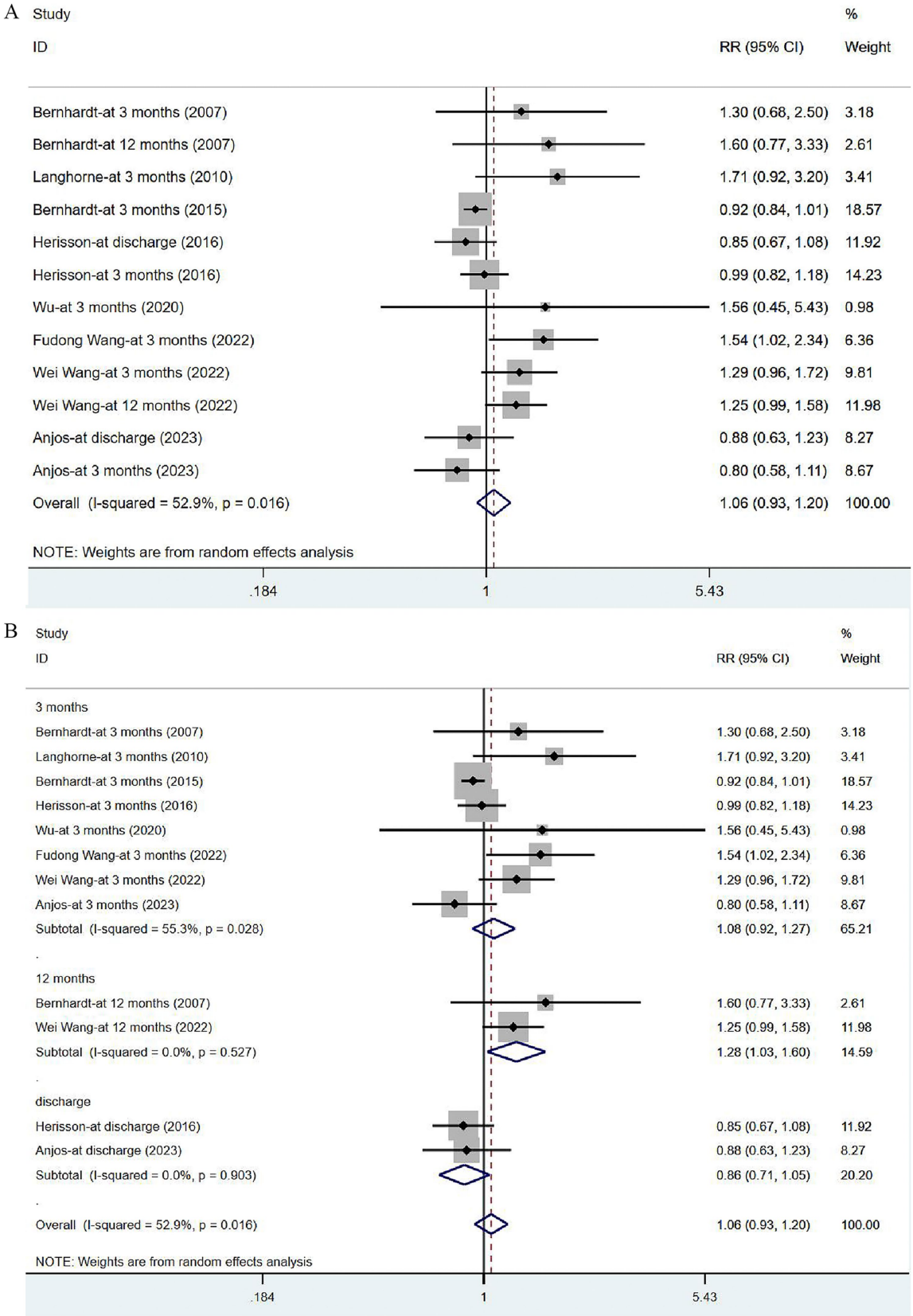

FIGURE 7
Forest plot of the disability degree. (A) Forest maps of meta-analysis of mRS. (B) Forest maps of subgroup analysis of mRS. (A) Comparison: the effect of VER on the mRS after stroke. Statistical method: Inverse-variance of the random effects model [relative risk (RR) and 95% confidence interval (CI)]. Very early rehabilitation (VER); modified Ranking Scale (mRS). (B) Comparison: the effect of VER on the mRS after stroke at different endpoints. Very early rehabilitation (VER); modified Ranking Scale (mRS); RR, risk ratio; 95% CI, 95% confidence interval.

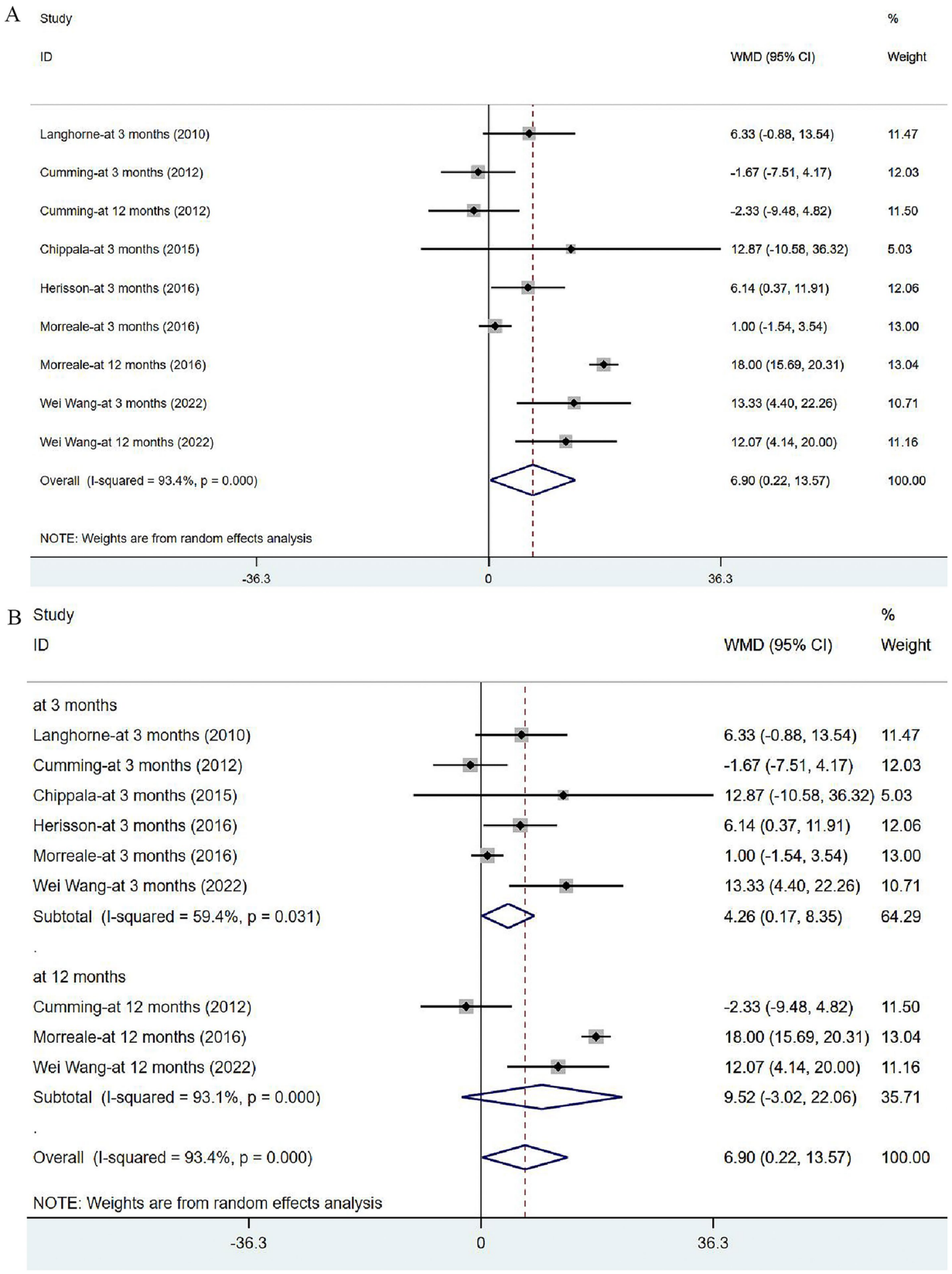

FIGURE 8
Forest plot of the daily living. (A) Forest maps of meta-analysis of BI. (B) Forest maps of subgroup analysis of BI. (A) Comparison: the effect of VER on BI. Statistical method: Inverse-variance of the random effects model [weighted mean difference (WMD) and 95% confidence interval (CI)]. Barthel Index (BI); very early rehabilitation (VER). (B) Comparison: the effect of VER on BI after stroke at different endpoints. Barthel Index (BI); very early rehabilitation (VER); weighted mean difference (WMD); 95% CI: 95% confidence interval.

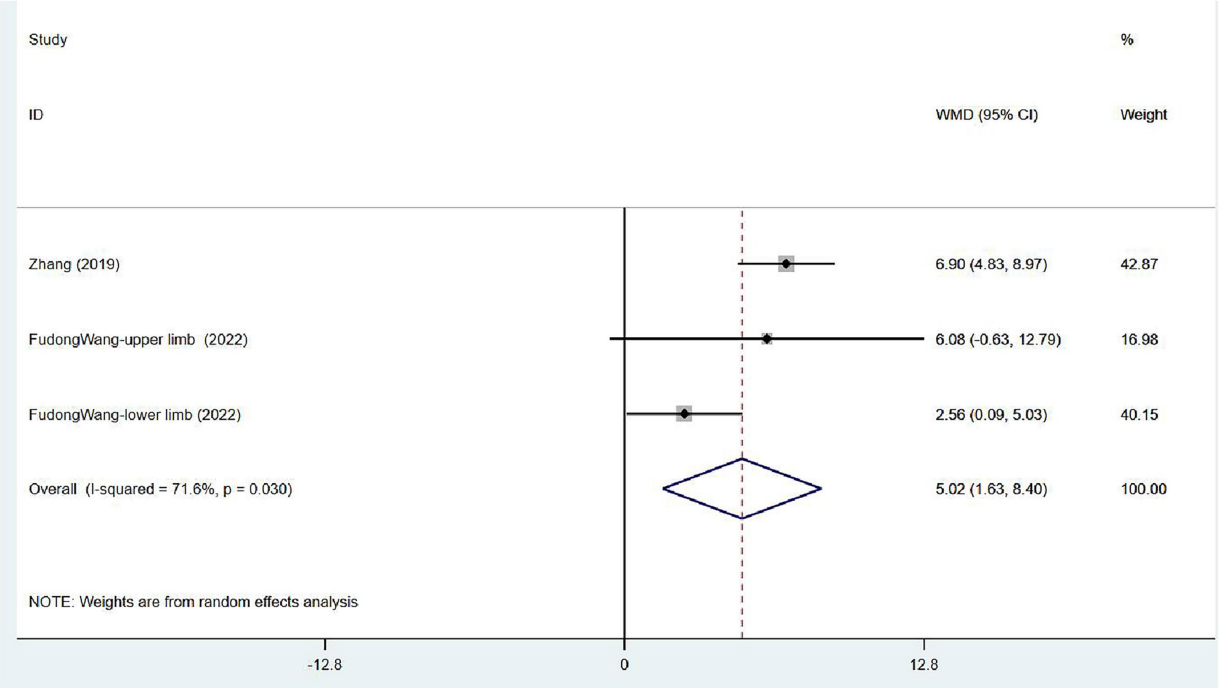

FIGURE 9
Forest plot of meta-analysis of limb motor function. Comparison: the effect of VER on FMA. Statistical method: Inverse-variance of the random effects model [weighted mean difference (WMD) and 95% confidence interval (CI)]. Fugl-Meyer assessment (FMA); very early rehabilitation (VER).

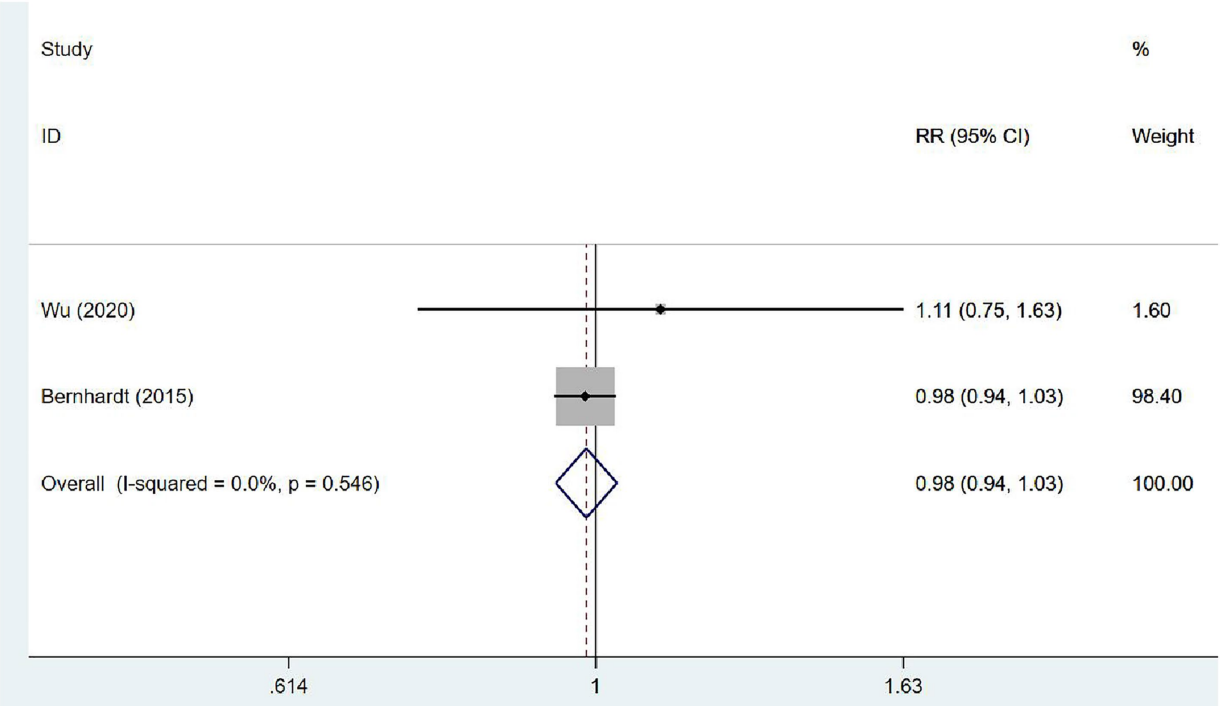

FIGURE 10
Forest plot of meta-analysis of the proportion of walking 50 m unassisted. Comparison: the effect of VER on the proportion of walking 50 m unassisted at 3 months after stroke. Statistical method: Inverse-variance of the fixed effects model [relative risk (RR) and 95% confidence interval (CI)]. very early rehabilitation (VER).

Complications arising from stroke can be categorized into those associated with immobility and neurological adverse events of stroke progression and current stroke, and the latter can be fatal for severely ill patients. Unlike patients recovering from surgery or other medical conditions like heart failure, asthma, or gastrointestinal bleeding, individuals with AIS are at an elevated risk for falls and costly hospital-acquired complications such as fractures, pneumonia, skin pressure ulcers, lower limb venous thrombosis, and pulmonary embolism (65, 66). The prevention of these complications is crucial not only for improving individuals' long-term quality of life but also for easing the societal healthcare burden. Physical exercise in the later stage plays a crucial role in maintaining health, aiding muscle recovery, and preventing the complications associated with prolonged bed rest (46, 48), but the optimal time for initiating rehabilitation in the acute phase of stroke remains uncertain. Furthermore, despite the expansion and construction of stroke units, there was insufficient evidence to determine whether the reduction in complications is owing to routine mobilization of standard care or early rehabilitation (67, 68). A prior meta-analysis revealed that VER did not increase the incidence of adverse events, which was consistent with the results in this study [RR = 0.89, 95% CI (0.79, 1.01)]. Subgroup analyses demonstrated that early rehabilitation lowered the incidence of complications in the late stage (at 3 and 12 months) after stroke [RR = 0.86, 95% CI (0.74, 0.99)], although the effect was not significant for the early period (during hospitalization or within 14 days) [RR = 0.99, 95% CI (0.79, 1.24)]. VER was demonstrated to have a lasting effect in reducing adverse events. A retrospective study showed that patients with severe disabilities were about 2.5 times more likely to develop complications than those with mild disabilities (69). In conclusion, the reduction of long-term complications after stroke can be attributed to the beneficial effects of early rehabilitation on recovery of physical activities, which can shorten the time of immobility. A very early rehabilitation trial (AVERT) demonstrated that the longer patients remained hospitalized, the greater their likelihood of experiencing mobility-related complications (70). Nevertheless, the causal association between hospital stay length and the occurrence of complications remains unraveled. It is hypothesized that early rehabilitation may mitigate post-stroke complications by shortening hospital stays. Due to limitations in the available data, complications were not categorized according to their mechanisms. Future research could clarify the correlation between early rehabilitation and immobility-related complications by systematically categorizing complications based on their underlying mechanisms.

Our findings proved the effectiveness of VER for the recovery of living ability and limb movement in stroke patients, mainly at three or 12 months in the subgroup analysis, and indicated that its effects are long-lasting. The mRS of 0–2 proportion and BI were employed to assess daily life ability and independence, which were indicative of the quality of life in older age. Previous systematical reviews have demonstrated that intensive rehabilitation or physiotherapy was beneficial to the improvement of physical performance (71, 72). The most rapid improvement was observed within the first 6 months after stroke (72, 73), which was similar to the results related to BI in the present analysis, and a significant increase was noted at 3 months after the stroke onset [WMD = 4.26, 95% CI (0.17, 8.35)]. Therefore, the rate of recovery of physical function after stroke is not uniform. In comparison to the previous meta-analysis, our study incorporated the FMA and the proportion of walking 50 m unassisted to evaluate limb mobility. Patients in the VER group exhibited a notable increase in FMA scores, which indicated a significant improvement in limb function recovery. However, it's important to acknowledge the limited scope of our analysis, as it was based on only two studies with differing assessment methodologies—one evaluating total scores and the other focusing on upper and lower limb function separately. Given the observed heterogeneity, these results should be interpreted with caution. VER stimulates marrow stem cells to differentiate into endothelial progenitor cells (12), thereby introducing angiogenesis in ischemic areas by boosting VEGF secretion (74, 75) and interacting with the expression of inflammatory factors in circulation. VER-induced increase of IF-10 and inhibition of TNF-α expression are not only associated with endothelial progenitor cells mobilization, but also play a significant role in anti-inflammation and neuroprotection during the acute phase of stroke (12). Furthermore, the brain is highly plastic after stroke because synaptic connections are formed and removed through constant activity (68), which proved that the recovery of nerve and following muscle function hinged on physical training. Biernaskie et al. conducted rehabilitation treatments for rats with cerebral middle artery occlusion at different times, and found that the recovery effect declined with delay of the start time of rehabilitation (76). This suggests that stroke recovery, which is contingent on the process in which a number of synapses re-establish connections and transmit signals (66), does have a time window. Therefore, the identification of the optimal time for initiating VER should be based on this window. However, determining the ideal early rehabilitation time after stroke remains challenging. Tong et al. conducted a study in which the experimental group received rehabilitation within 24 h, while the control group received it within 24–48 h. Their findings indicated that rehabilitation initiated at 48 h after stroke was beneficial, whereas VER within 24 h did not produce favorable outcomes at 3 months (77). Research on rats undergoing early training within 24 h showed increased apoptotic cell death (78, 79), which leads to enlarged infarcts.

In terms of recovery related to ADLs after stroke, both cognitive and motor tasks, especially those involving postural balance and walking, must be considered. A cross-sectional observational study involving 163 community-based chronic stroke survivors revealed that over half of participants had somatosensory impairments in the lower limb, especially in the distal regions, which was strongly correlated with the risk of falling (80). Proprioceptive training, which focuses on the body's ability to recognize joint position and body movement, could better mobilize patients' autonomy and cognitive function than traditional limb motor rehabilitation (81). Task-oriented exercises, with its increasing cognitive load, aided participants in real-world activities (82), and exhibited beneficial effects on proprioception, impaired gait, and spasticity (83). Constant sensory input of the limbs stimulates proprioception and decreases muscle stiffness (83). Published studies demonstrated that proprioceptive training, and dual-task exercises (cognitive and motor tasks) could significantly improve both balance and autonomy (81, 84, 85). However, it should also be noted that in the very early stage of AIS, the dual-task training on patients with limb weakness may lead to safety problems such as falls and sprains. In addition, speech training was proved to be crucial for addressing communication impairments (dysarthria) in clinical practice and was an important part of post-stroke rehabilitation, because people with dysarthria would have no social participation and be ignored in communication (86). Therefore, early rehabilitation after stroke should be comprehensive and cover motor, cognition, proprioception and speech, thereby offering a more comfortable experience for the post-stroke population. A personalized

and enriched rehabilitation program can both improve adherence and mitigate the negative emotion caused by hemiplegia and dysarthria.

The present meta-analysis has several limitations. First, the strict criteria adopted to define early rehabilitation time led to a reduced number of eligible studies, so the overall sample size was small. Moreover, the robustness of the subgroup analysis results may be compromised due to the limited number of studies available. Second, many studies were excluded from the quantitative synthesis due to different data types of outcome indicators between studies, which may have resulted in bias. Third, the included studies varied in the duration, dose, intensity, and frequency of rehabilitation treatments, and the final results might have been influenced by multiple variables. Fourth, in some studies, out-of-bed activities may be initiated too early in the control population, so there existed confusion about whether the result was influenced by standard care intervention. Fifth, in this research, a 24-h time threshold was not set for comparing the prognosis of VER initiated within 24 h versus 24–48 h. Lastly, stroke type and stroke treatment in the acute phase (intravenous thrombolysis, embolectomy, usual medication) were not systematically categorized due to limited studies.

5 Conclusion

In conclusion, VER could improve ADLs, lower the incidence of long-term complications in stroke survivors, and maintain such effectiveness. However, premature and overly intensive rehabilitation may elevate the risk of death in AIS patients in the acute phase. Statistics revealed that a growing number of patients with severe symptoms tended to receive rehabilitation in post-stroke specialized units, which is driven by demographic trend toward an aging population (69). Therefore, achieving both safety and efficacy in VER necessitates a comprehensive consideration of multiple factors and the development of tailored strategies. Attention should be paid not only to the initiation time of rehabilitation treatment in the acute phase of AIS, but also to the cultivation of physical exercise habits after discharge.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YL: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. ZL: Methodology, Writing – review & editing. YJ: Writing – review & editing. JC: Formal analysis, Investigation, Writing – review & editing. CZ: Writing – review & editing. LL: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1423517/full#supplementary-material

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Improvements in upper extremity isometric muscle strength, dexterity, and self-care independence during the sub-acute phase of stroke recovery: an observational study on the effects of intensive comprehensive rehabilitation

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Background: Stroke often impairs upper extremity motor function, with recovery in the sub-acute phase being crucial for regaining independence. This study examines changes in isometric muscle strength, dexterity, and self-care independence during this period, and evaluates the effects of a comprehensive intensive rehabilitation (COMIRESTROKE).

Methods: Individuals in sub-acute stroke recovery and age- and sex-matched controls were assessed for pre- and post-rehabilitation differences in primary outcomes (grip/pinch strength, Nine Hole Peg Test [NHPT], Action Research Arm Test [ARAT]). COMIRESTROKE's effects on primary and secondary outcomes (National Institute of Health Stroke Scale [NIHSS], Modified Rankin Scale [MRS], Functional Independence Measure [FIM]) were evaluated. Outcomes were analyzed for dominant and non-dominant limbs, both regardless of impairment and with a focus on impaired limbs.

Results: Fifty-two individuals with stroke (NIHSS 7.51 ± 5.71, age 70.25 ± 12.66 years, 21.36 ± 12.06 days post-stroke) and forty-six controls participated. At baseline, individuals with stroke showed significantly lower strength (dominant grip, key pinch, tip-tip pinch, $p_{adj} < 0.05$), higher NHPT scores ($p_{adj} < 0.05$), and lower ARAT scores ($p_{adj} < 0.001$). COMIRESTROKE led to improvements in dominant key pinch, non-dominant tip-tip pinch, NHPT, and both dominant and non-dominant ARAT ($p_{adj} < 0.05$). Notably, non-dominant key pinch improved significantly when considering only impaired hands. Pre- and post-test differences between groups were significant only for ARAT (both

limbs), even after adjustment ($p_{adj} < 0.05$). All secondary outcomes (NIHSS, MRS, FIM) showed significant improvement post-COMIRESTROKE ($p_{adj} < 0.001$).

Conclusion: Individuals with stroke exhibit reduced muscle strength and dexterity, impairing independence. However, comprehensive intensive rehabilitation significantly improves these functions. Data are available from the corresponding author upon request and are part of a sub-study of NCT05323916.

KEYWORDS

ischemic stroke, rehabilitation, physiotherapy, isometric grip strength, maximum strength during key, tripod, and tip-tip pinch, dexterity

Introduction

Stroke is a leading cause of physical impairments (1, 2). Up to 80% of post-stroke survivors have impairment of the upper extremity (2–6). Its most common symptom is paresis (3, 7, 8), which is characterized by reduced muscle strength (caused by reduced motor unit recruitment and muscle changes as atrophy (8)) and subsequently by loss or limitation of function in muscle control or movement or mobility (3, 5, 8–12) which can subsequently negatively affect self-sufficiency and quality of life (2, 8, 13). Due to upper extremity impairment, more than 50% of individuals post-stroke require assistance (usually mild to moderate) in dressing or bathing, and the majority require full assistance in some activities of daily living, such as meal preparation or housekeeping. Only a few of them can return to work and devote themselves to family and leisure activities as they did before the stroke (1, 7, 14, 15). The therapeutic influence of upper limb impairment is, therefore, very important from the point of view of maintaining functional independence (2, 5).

Promoting functional recovery of the impaired upper extremities is one of the major goals of stroke rehabilitation (3). Most motor recovery occurs early, typically plateauing around 3 months after stroke (16–18), due to processes of motor control and learning that are shared with the mechanisms of adaptive functional reorganization during spontaneous recovery (3, 19–21). These recovery processes can be enhanced through appropriate rehabilitation, which involves applying various intrinsic or extrinsic stimuli (6) aimed at remodeling the brain's plastic and adaptive processes (22). Appropriate rehabilitation encompasses a range of techniques specifically designed to improve upper limb function following a stroke (23, 24). Such approaches include bilateral training (4), constraint-induced movement therapy (25), electrical stimulation (26), repetitive task training (15, 23), reaching distance and speed instructions (27), and robotics (1).

While key rehabilitation principles, such as therapy intensity (23, 28–30) and comprehensiveness (24, 31, 32), are recognized as important, their effects on upper extremity function remain insufficiently explored, as most studies focus on therapies specifically targeting upper extremity function (1, 4, 15, 23). Therefore, this study aims to evaluate the impact of a comprehensive inpatient rehabilitation program (COMIRESTROKE) (33) among individuals in sub-acute stroke recovery.

We measured strength as a predictor of motor performance, functional ability, and recovery following rehabilitation. The methodology for assessing muscle strength in individuals with central motor neuron impairment is not straightforward. While some researchers consider isokinetic dynamometry to be the "gold standard" (34) due to its ability to capture the dynamic nature of functional tasks (7, 35), others advocate for evaluating isometric muscle strength as a more suitable approach (10, 16, 36). Isometric strength testing is often regarded as a more sensitive measure of motor performance, despite its inherent variability (7), because it is specifically designed to evaluate initial upper limb recovery and serves as a reliable prognostic indicator for future recovery (16). Additionally, it has demonstrated strong reliability and a close association with motor performance (10). Therefore, we opted for isometric muscle strength testing in our study to leverage these advantages.

On the other hand, hand-held dynamometry assesses only a single aspect of function; it can monitor the level of motor dysfunction and provide key information about the function of the motor cortex. However, the results cannot be generalized to functional movement ability or the capacity for rehabilitation (12). To provide a more comprehensive evaluation, we also included more functionally relevant tests (7) focused on dexterity, such as the Nine Hole Peg Test (NHPT) and the Action Research Arm Test (ARAT), in our primary outcomes.

Additionally, we were interested in exploring whether improvements in upper limb impairment would impact the ability to maintain independence. To address this, we included the Functional Independence Measure (FIM) as a secondary outcome.

Although the literature clearly indicates that upper extremity function and subsequent self-care independence are impaired in individuals with stroke, no study has yet directly compared clinical parameters with a control group. Therefore, in our study, we included individuals of similar age and sex without significant neurological or orthopaedic conditions as a control group. This approach aimed to strengthen the validity of our results and support the reliability of the measurements.

The goals of this study were:

1 To characterize the clinical involvement of the upper extremity in individuals during the sub-acute phase of stroke recovery and compare it with control groups.

We hypothesized that there would be significant differences in primary outcomes between individuals with stroke and the control groups. Additionally, we anticipated a correlation between primary and secondary outcomes in individuals with stroke.

2 To evaluate the effect of the COMIRESTROKE rehabilitation program.

We hypothesized that there would be no significant changes between the first and second measurements in the control group. In contrast, we expected to see significant improvements in primary outcomes before and after rehabilitation in individuals with stroke, with notable differences between the stroke and control groups.

Methods and analysis

Study design

This article analyses data collected between June 1, 2020 to July 31, 2023 as a sub-study of the NCT05323916 (33). Primary outcomes (isometric grip and pinch force, NHPT, and ARAT) were assessed twice: in individuals with stroke before and after 3 weeks of COMIRESTROKE, and in controls in the same interval without rehabilitation. Secondary outcomes (National Institute of Health Stroke Scale, the Modified Rankin Scale, and FIM) were investigated only in individuals with stroke before and after rehabilitation.

Participants

Individuals in the sub-acute phase of stroke recovery hospitalised in the Stroke Center of the Thomayer University Hospital were included by a neurologist based on these *criteria*: adults (18–89 years) after the first ischemic stroke in the early sub-acute phase (16, 17), with a slight to moderately severe disability (2–5 on the Modified Rankin Scale). People with low levels of consciousness, severe cognitive decline, and severe medical problems with a poor prognosis (37) were excluded.

As controls, individuals hospitalized at the same hospital were selected by a medical doctor to be as similar as possible to the post-stroke individuals in terms of sex and approximate age. These controls were admitted for planned examinations or scheduled rehabilitation aimed at improving musculoskeletal pain due to vertebropathy or enhancing their physical or mental condition. Importantly, they were not hospitalized for any acute reason, and any serious neurological or orthopaedic diseases.

Interventions

Individuals who experienced a stroke participated in the COMprehensive Intensive REhabilitation program after STROKE (COMIRESTROKE). This program, overseen by a medical doctor, provided personalized therapies tailored to each patient. The rehabilitation combined physiotherapeutic techniques (with at least 1 hour daily), occupational therapy, psychotherapeutic approaches, and logopaedic techniques, all delivered in an intensive format. The therapy sessions lasted 4 h each day, 6 days a week, over a 3-week period (38). The treatment in each session was led by educated and experienced therapists at the Department of Rheumatology and Rehabilitation, Third Faculty of Medicine, Charles University, and Thomayer University Hospital.

Controls underwent standard inpatient hospitalization without any pre-defined rehabilitation.

Assessment

Demographic and anamnestic data, including sex, age, weight and height, handedness (39), and number of days after the stroke event, were obtained after enrolment in the study.

An independent and certified Clinical Evaluator assessed the primary and secondary outcomes before and after the COMIRESTROKE program.

Primary outcomes

Isometric grip strength was measured using a Jamar Hydraulic Hand Dynamometer (40). The measurement was conducted while the subject was seated on a chair with their lower limbs resting on the floor. The upper limbs were positioned with the arm in adduction, the elbow flexed at 90°, the forearm and wrist in a neutral position, and the fingers slightly extended. The dynamometer handle can be adjusted to five grip positions (9, 12, 14.5, 17, and 20 cm) to accommodate different hand sizes (41). In each of the five positions, the maximum isometric force was measured three times, and the average of these measurements was calculated. The highest value obtained across the positions was selected, with a higher value indicating better grip strength.

Isometric maximum strength during key, tripod, and tip-tip pinch were measured by a Pinch Gauge dynamometer. The measurement took place in the same position as during the measurement of isometric grip strength, only the examiner held the dynamometer to prevent it from falling. The isometric force was measured three times for each of three grip pinchs, and the average isometric force was recorded (a higher value means a better result) (40).

Action Research Arm Test is a 19-item observational measure assessing upper extremity performance (coordination, dexterity, and functioning). A higher score means better functioning (42).

The Nine Hole Peg Test is used to measure finger dexterity. A client takes the pegs from a container, one by one, and places them into the holes on the board as quickly as possible. Shorter times reflect better functioning (43).

Secondary outcomes

The National Institute of Health Stroke Scale measures stroke-related neurological deficit (44) on a 15-item scale from 0 to 42 (higher scores indicating greater severity).

The Modified Rankin Scale (45) is used to categorize the level of functional independence with reference to pre-stroke activities on a scale from 0 to 5 (higher scores indicating greater disability).

Functional Independence Measure (46) evaluates independence for self-care (e.g., sphincter control, transfers, locomotion, communication, social cognition). The higher the score (between 18 and 126), the more independent the person is in performing the task.

Statistical analysis

We tested for differences in basic descriptive characteristics between individuals with stroke and controls. In the case of binary variables – sex and laterality, Pearson's chi-squared test was used, while for continuous variables, two-sample t-tests were employed. Outcomes were presented separately for the dominant and non-dominant limbs. Differences between individuals with stroke

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TABLE 1 The CONSORT diagram of participant recruitment.

Individuals with stroke		Controls
140	Screened	125
57	Met inclusive criteria	49
57	Consented to participate and underwent first examination	47
52	Completed the study	46
4 Discharged at one's own request (subjective opinion that one does not need to be hospitalised/ rehabilitated) 1 Parched rehabilitation due to Covid 19	Reasons for not completing the second measurement	1 Discharged before a second examination was organised

TABLE 2 Sample characteristics.

	Individuals with stroke		Controls		*p*-value*
	M	F	M	F	
Sex	28	24	21	25	0.544
	R	L	R	L	
Laterality	47	3	41	5	0.622
	R	L			
Affected side	20	27			
	Mean	SD	Mean	SD	
Age (years)	70.25	12.66	72.76	15.20	0.380
Weight (kg)	80.59	23.22	75.72	20.63	0.277
Height (cm)	168.63	13.97	169.28	17.86	0.842
Days after stroke	21.36	12.06			

*Testing difference between individuals with stroke and controls (in case of binary variables—sex and laterality, Pearson chi-squared test is used, for continuous variables two-sample *t*-test is used).
R, right; L, left; M, male; F, female; SD, standard deviation.

and controls were first analyzed regardless of limb impairment, then with a focus on impaired limbs. A side was considered impaired if the neurologist assigned a minimum score of 1 on the Motor Function Arm scale, a sub-scale of the NIHSS, which ranges from 0 to 9.

Differences between individuals with stroke and controls in measured outcomes at baseline (after the first measurement) were tested using two-sample t-tests. All *p*-values were adjusted for multiple comparisons using the Benjamini-Hochberg correction.

The difference between pre-scores (first measurement) and post-scores (second measurement) was tested separately for both groups (individuals with stroke and controls) using paired t-tests. Then, two-sample t-tests were used to assess pre-post differences in scores between controls and individuals with stroke. Adjustment for multiple comparisons was applied.

To evaluate associations between measured outcomes at baseline for individuals with stroke, Pearson's correlation coefficient *r* was used. The differences were evaluated as statistically significant if $p_{adj} < 0.05$. The analysis was performed using the free statistical software R, version 4.3.2 (37), and its corresponding packages.

Results

Participants' characteristic

Table 1 shows the CONSORT diagram of participant recruitment. Fifty-two individuals with stroke (NIHSS 7.51 ± 5.71, age 70.25 ± 12.66 years, days after stroke onset 21.36 ± 12.06) and forty-six controls were included in the study. There were no significant differences between groups in basic characteristics (see Table 2). Fifteen individuals with stroke had impaired right side, 21 had left side, 4 had bilateral impairment, and 8 did not have detectable impairment on NIHSS. In four cases, information about impairment was not available. Among the 52 subjects, 18 had impairment in their dominant hand, 31 had no impairment, and 3 had unknown impairment status of their dominant hand. For the non-dominant hand, 28 subjects had impairment, 21 had no impairment, and 3 had unknown impairment status.

Among the subjects from experimental group, 47 were right-handed and 3 were left-handed before their stroke; hand dominance was not determined for 2 subjects. In the control group, 41 were right-handed and 5 were left-handed.

The clinical involvement of the upper extremity of individuals in the sub-acute phase of stroke recovery.

Individuals with stroke had more clinically affected both dominant (D) and non-dominant (ND) upper limbs, documented by significantly lower strength (grip D mean difference −4.99 ± 10.84, key pinch D mean difference −1.01 ± 1.97, tip-tip pinch D mean difference −0.96 ± 1.57, and tip-tip pinch ND mean difference −0.74 ± 1.77), higher value in NHPT D (mean difference 19.51 ± 26.45) and NHPT ND (mean difference 12.47 ± 17.04) and lower scores in ARAT D (mean difference −11.30 ± 15.09) and ARAT ND (mean difference −17.04 ± 18.72), see Table 3.

Non-dominant NHPT (r = −0.45) non-dominant grip (r = 0.37), both key (r = 0.33 for dominant, r = 0.37 for non-dominant) and tip-tip pinch (r = 0.33 for dominant, r = 0.35 for non-dominant) correlated well with FIM.

The effect of the COMIRESTROKE

COMIRESTROKE had a positive effect on primary outcomes: The improvement was significant in key pitch D (0.40 ± 0.94, $p_{adj} = 0.027$) and tip-tip pinch ND (0.39 ± 0.67, $p_{adj} = 0.015$), also, the mean NHPT ND decreased by 8.43 ± 18.46 ($p_{adj} = 0.049$), mean ARAT D increased by 3.36 ± 7.37 ($p_{adj} = 0.015$) and mean ARAT ND increased by 3.17 ± 6.39 ($p_{adj} = 0.0015$); also, secondary outcomes, NIHSS, MRS, and FIM improved significantly ($p_{adj} < 0.001$), see Table 4.

As expected, the improvement is more evident when only impaired limbs are considered, as we can see the pre-post differences are often larger in absolute value (Table 5). However, some differences

TABLE 3 Difference between individuals with stroke and controls in pre-test.

	Individuals with stroke			Controls			Individuals with stroke vs. controls			
	N	Mean	SD	N	Mean	SD	Diff	SD_{both}	Stat	$p\text{-value}_{adj}$
NHPT D	42	45.88	35.07	46	26.37	6.78	19.51	26.45	3.55	0.004
NHPT ND	32	40.70	22.94	46	28.23	8.32	12.47	17.04	2.94	0.013
grip D	45	20.55	9.51	46	25.54	11.57	−4.99	10.84	−2.25	0.046
grip ND	38	18.86	10.50	46	24.05	12.07	−5.19	11.61	−2.11	0.057
key pinch D	45	4.24	2.01	46	5.25	1.81	−1.01	1.97	−2.51	0.028
key pinch ND	38	4.49	2.73	46	4.80	1.99	−0.31	2.34	−0.58	0.612
tripod pinch D	44	2.84	1.50	46	3.15	1.29	−0.30	1.40	−1.02	0.371
tripod pinch ND	37	2.93	1.91	46	2.98	1.34	−0.05	1.61	−0.15	0.885
tip-tip pinch D	44	3.25	1.57	46	4.21	1.43	−0.96	1.57	−3.01	0.010
tip-tip pinch ND	35	3.10	1.89	46	3.84	1.62	−0.74	1.77	−1.85	0.091
ARAT D	50	45.70	19.48	46	57.00	0.00	−11.30	15.09	−4.10	0.001
ARAT ND	47	39.96	23.55	46	57.00	0.00	−17.04	18.72	−4.96	< 0.001

SD, standard deviation; adj, adjusted; D, dominant; ND, non-dominant; NHPT, Nine Hole Peg Test; ARAT, Action Research Arm Test.

are not significant due to the small sample size, muscle strength improved significantly in the key pinch ND (0.59 ± 0.66, $p_{adj} = 0.034$), and ARAT ND (5.48 ± 8.11, $p_{adj} = 0.034$) of impaired non dominant hand, see Table 5. The improvement is less evident in non-impaired limbs (Table 6).

As expected, clinical characteristics did not change in the control group between the first and second examinations. The pre-post differences between the two groups were significant only in ARAT D and ND, even after adjusting ($p_{adj} < 0.05$) (Table 4).

Discussion

In this article, we present the results of a sub-study focused on upper limb function. This sub-study is part of the randomized trial NCT05323916, for which the estimated sample size was calculated to be 280 participants. This sample size allows for the demonstration of differences between four groups (70 participants per group) using the WHO Disability Assessment Schedule 2.0 (47). For this sub-study, the sample size was not specifically pre-calculated. However, our sample size matches (4, 23, 48, 49), or even exceeds (1, 15, 50), the sample sizes of other studies addressing this issue.

Although we attempted to assign participants to both groups evenly, perfect 1:1 matching was not possible due to discontinuations from the study for various reasons. This resulted in slightly unbalanced groups: 46 post-stroke patients and 52 controls. Consequently, the groups were analyzed as independent samples in the statistical analysis rather than as matched pairs. To ensure comparability, statistical tests were performed to evaluate whether the groups differed in basic characteristics. Specifically, t-tests were used for age, weight, and height, and chi-square tests were used for sex and laterality.

It is debatable whether we can consider the population selected for our control group to be healthy. Although individuals with neurological or orthopaedic conditions were excluded, the participants were hospitalized, albeit for preventive reasons. They were people of a similar age to those in the experimental group, which suggests that various health issues may be present in such a population.

The age range in our study was quite broad—35 to 89 years for patients and 33 to 93 years for controls. However, most participants fell into the older age categories. Due to the uneven distribution across different age groups, we did not analyze the differences in response to stroke and procedures performed in our study with respect to age. As well, due to low samples, we did not analyze the differences with respect to gender.

Our hypothesis that individuals with stroke have greater upper extremity impairment than controls was confirmed. However, we were surprised to find that significant differences in muscle strength between stroke patients and controls were evident only after adjusting for grip, key, and tip-tip pinch strength in the dominant hand (regardless of impairment). These findings did not show more pronounced differences compared to the control group, as we had expected to see greater disparities across a broader range of parameters.

Only few studies (49, 51) consider the dominance of the limbs on the affected side in individuals with stroke, although it may play a role. Most studies compare impaired and unimpaired upper extremities independently on upper extremity dominance (10, 36, 43, 49). Gilbertson and Barber-Lomax (52) found no significant difference between the dominant and non-dominant upper limbs; however, the variability may be greater in the values for the non-dominant upper limb, making it more difficult to detect significant differences with medium-sized samples.

Across studies, stroke survivors have lower muscle strength, but this varies depending on neurological deficit, post-stroke time, and

TABLE 4 Difference between individuals with stroke and controls in pre-test post-test differences.

	Individuals with stroke								Controls								Individuals with stroke vs. controls			
		PRE		POST		PRE-POST				PRE		POST		PRE-POST						
	N	Mean	SD	Mean	SD	Mean	SD	p-value$_{adj}$	N	Mean	SD	Mean	SD	Mean	SD	p-value$_{adj}$	Diff	SD$_{both}$	Stat	p-value$_{adj}$
NHPT D	38	46.77	36.79	36.46	13.82	−10.31	34.17	0.122	45	26.41	6.85	26.87	8.33	0.47	3.75	0.738	−10.78	23.74	−1.93	0.145
NHPT ND	29	41.97	23.76	33.55	10.66	−8.43	18.46	0.049	45	28.27	8.41	28.29	7.68	0.02	5.24	0.976	−8.45	12.83	−2.40	0.090
grip D	41	20.70	9.50	21.57	10.09	0.88	2.93	0.122	45	25.66	11.67	25.41	12.68	−0.25	4.68	0.899	1.13	3.96	1.36	0.307
grip ND	35	18.33	10.55	19.10	10.06	0.76	3.11	0.235	45	24.19	12.16	24.46	12.00	0.27	2.31	0.738	0.50	2.68	0.79	0.650
key pinch D	41	4.24	2.10	4.64	2.10	0.40	0.94	0.027	45	5.28	1.83	5.40	1.90	0.12	0.71	0.738	0.28	0.83	1.57	0.241
key pinch ND	35	4.34	2.53	4.43	2.28	0.09	0.97	0.700	45	4.79	2.01	4.94	2.02	0.14	0.73	0.738	−0.05	0.84	−0.27	0.869
tripod pinch D	40	2.88	1.56	3.00	1.33	0.13	1.18	0.676	45	3.16	1.31	3.26	1.35	0.10	0.82	0.738	0.03	1.00	0.12	0.902
tripod pinch ND	33	2.77	1.79	2.74	1.51	−0.03	0.93	0.877	45	3.00	1.35	2.92	1.46	−0.08	0.83	0.761	0.05	0.87	0.26	0.869
tip-tip pinch D	40	3.25	1.64	3.30	1.57	0.05	0.76	0.768	45	4.22	1.45	4.31	1.62	0.10	0.73	0.738	−0.05	0.74	−0.31	0.869
tip-tip pinch ND	33	3.16	1.92	3.55	1.94	0.39	0.67	0.015	45	3.86	1.64	3.88	1.69	0.03	0.83	0.927	0.36	0.78	2.14	0.107
ARAT D	45	45.71	19.25	49.07	17.90	3.36	7.37	0.015	45	57	0	57	0	0	0		3.36	5.45	3.05	0.023
ARAT ND	41	41.66	22.22	44.83	19.76	3.17	6.39	0.015	45	57	0	57	0	0	0		3.17	4.66	3.18	0.023
NIHSS	43	7.51	5.71	4.74	4.31	−2.77	2.02	< 0.001												
Modified Rankin scale	45	3.69	0.76	3.07	0.99	−0.62	0.65	< 0.001												
FIM	44	75.59	24.58	92.43	23.56	16.84	10.41	< 0.001												

SD, standard deviation; adj, adjusted; D, dominant; ND, non-dominant; NHPT, Nine Hole Peg Test; ARAT, Action Research Arm Test.

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TABLE 5 Pre-test post-test differences in individuals with stroke on the impaired upper extremity.

	Post-stroke patients with impaired upper extremity							
		PRE		POST		PRE-POST		
	N	Mean	SD	Mean	SD	Mean	SD	p-value$_{adj}$
NHPT D	10	57.96	27.93	46.06	21.76	−11.90	21.75	0.157
NHPT ND	10	60.39	31.66	40.27	12.47	−20.11	28.12	0.086
grip D	12	14.96	9.82	14.38	10.95	−0.58	3.16	0.537
grip ND	15	12.07	6.77	13.64	7.45	1.58	3.02	0.094
key pinch D	11	3.36	2.62	4.02	2.78	0.65	0.84	0.068
key pinch ND	15	2.87	1.76	3.46	1.90	0.59	0.66	0.034
tripod pinch D	11	2.12	1.95	2.35	1.60	0.23	1.08	0.537
tripod pinch ND	13	1.72	1.44	2.14	1.55	0.42	0.69	0.086
tip-tip pinch D	11	2.53	2.01	2.73	2.08	0.20	0.67	0.423
tip-tip pinch ND	13	2.01	1.52	2.63	1.75	0.62	0.81	0.053
ARAT D	15	27.33	23.60	34.87	25.68	7.53	10.78	0.053
ARAT ND	21	28.76	24.40	34.24	22.89	5.48	8.11	0.034

SD, standard deviation; adj, adjusted; D, dominant; ND, non-dominant; NHPT, Nine Hole Peg Test; ARAT, Action Research Arm Test.

TABLE 6 Pre-test post-test differences in individuals with stroke on the unimpaired upper extremity.

	Post-stroke patients with unimpaired upper extremity							
		PRE		POST		PRE-POST		
	N	Mean	SD	Mean	SD	Mean	SD	p-value$_{adj}$
NHPT D	27	43.41	39.74	33.44	7.41	−9.98	38.67	0.287
NHPT ND	19	32.28	9.44	30.00	7.78	−2.28	4.36	0.212
grip D	28	23.25	8.53	24.79	8.23	1.54	2.68	0.064
grip ND	20	23.03	10.54	23.18	9.95	0.15	3.11	0.907
key pinch D	29	4.62	1.83	4.92	1.80	0.30	0.98	0.269
key pinch ND	20	5.45	2.49	5.17	2.30	−0.28	1.01	0.297
tripod pinch D	28	3.21	1.32	3.29	1.15	0.08	1.26	0.874
tripod pinch ND	20	3.45	1.68	3.13	1.38	−0.32	0.96	0.269
tip-tip pinch D	28	3.58	1.42	3.57	1.31	−0.02	0.80	0.907
tip-tip pinch ND	20	3.90	1.81	4.14	1.86	0.24	0.54	0.234
ARAT D	29	54.93	5.72	56.14	3.39	1.21	3.62	0.250
ARAT ND	20	55.20	6.01	55.95	4.02	0.75	2.17	0.269

SD, standard deviation; adj, adjusted; D, dominant; ND, non-dominant; NHPT, Nine Hole Peg Test; ARAT, Action Research Arm Test.

other factors. For example, Lang et al., (49) assessed individuals in the acute phase (±9.5 compared to our study ±21.6 days post-stroke) with a lower neurological deficit on NIHSS (5.3 ± 1.8 compared to our study 7.51 ± 5.71) and documented lower grip strength (9.6 ± 10.5 compared to our study 20.55 ± 9.51). Similar values of the affected grip and pinch as in our study documented by Chen et al., (43) in people with similar upper limb impairment according to NHPT (60.1 ± 38.2 compared to our study 57.96 ± 27.93).

The values between studies are essentially incomparable because authors use different units (36, 40, 53), different methodologies (10), use normalized relative strength (10). Although it is recommended not to use the unaffected upper extremity as a control group (8), only a few studies compared results with a healthy control group. For comparison, it is also possible to use normative data (52, 53); for example, compared to British norms, our controls have lower muscle strength (52). However, our controls cannot be considered a healthy

population because they were hospitalized for some reason in our hospital, although serious neurological and orthopedic diseases were excluded.

While the difference when comparing muscle strength parameters between individuals with stroke and controls in our study is not significant for non-dominant hand, clinical tests (ARAT, NHPT) show significant differences for both dominant and non-dominant hands.

COMIRESTROKE was associated with an improvement of both primary and secondary outcomes. The primary outcomes improved significantly, even after adjustment: tip-tip pinch of the impaired non-dominant hand, and ARAT of both dominant and non-dominant hand.

Demonstrating correlations between primary and secondary outcomes further confirms the consistency of our findings and their alignment with existing literature (54, 55). The relationship between the ARAT and the FIM has been explored in detail by Rabadi and Rabadi (55). The authors appropriately addressed multiple comparisons, considering the established collinearity between the NHPT and the ARAT (54), as well as the well-documented relationships between grip strength, the ARAT, and the NHPT.

When comparing our results to published Minimal Clinically Important Differences (MCID), they are less compelling, highlighting another limitation of this study. Specifically, for grip muscle strength, there was no significant change, with our findings being well below the MCID: 5 kg for the dominant hand (our study showed a change of −0.58 kg) and 6.2 kg for the non-dominant upper extremity (our study showed a change of 1.58 kg) (49). Unfortunately, we cannot evaluate changes in pinch strength in the context of MCID, as these values have not yet been established.

The greater improvement of the affected limb, which was non-dominant, surprised us and contradicted with opinion of Langan and van Donkelaar (50), who thought that people with the dominant hand affected by stroke have an advantage in improving the mobility of the more affected hand compared to those individuals with the non-dominant hand affected by stroke. Our results, on the other hand, align with a study where the highest median percent improvement in the affected non-dominant upper extremity was observed for grip strength (51).

We attribute this to the fact that in our study, we did not provide targeted therapy for upper extremity function but rather a comprehensive intensive rehabilitation. As a result, the rehabilitation did not specifically focus on improving upper extremity function or on the unique roles of each limb, such as enhancing dexterity in the dominant upper extremity or strengthening the non-dominant upper extremity for stabilization.

However, we consider the improvement in primary outcomes, mainly in ARAT (from 27.33 ± 23.60 to 34.87 ± 25.68), to be important, especially because it occurred after a complex intensive program that was not aimed at improving upper extremity function. The mean improvement of ARAT in our study corresponds to the improvement in the experimental group in other studies (15, 23) evaluating the effect of the targeted treatment on upper extremity function (the Repetitive Facilitative Exercise Program). On the other side, another kind of targeted therapy, aimed at improving the function of the affected upper extremity (low and high intensity of Constraint-induced movement therapy) can lead to significant improvement of ARAT (from 19.65 ± 3.73 to 36.20 ± 4.05 in 14 days) (48). Notably in an upper limb targeted therapy patients were stratified by the severity of the post-stroke arm-hand impairment and found that the sub-group of patients with a moderately affected arm-hand presented with best results regarding the ARAT and the Fugl-Meyer Motor Assessment (56).

Our results are consistent with the literature and confirm that ARAT is a suitable tool to predict improvement in individuals with stroke (9, 57), despite the fact that this assessment is limited by the use of an ordinal scale (3). However, its advantages are strong psychometric properties, fast administration (7) and bringing information about a patient's upper limb capacity by mimicking activities of daily living (57).

The greatest improvement was observed in the secondary outcomes: neurological impairment measured by the NIHSS, disability assessed using the MRS, and functional independence evaluated by the FIM. The improvement in FIM in our study (16.84 ± 10.41) was greater than in a study that reported a mean difference of 2.70 (4), or in a study where the change was 1.00 (1). Both studies (1, 4) specifically aimed to influence upper limb function while simultaneously assessing the impact on independence using FIM. However, the MCID, defined as 22 for stroke survivors (58), was not achieved in our study either.

Although the probands in both studies (1, 4) were young (50.7–55.51 years versus 70.25 ± 12.66 in our study), probably due to the severity of the disability (114.3–119.4 points on FIM versus 75.59 ± 24.58 point in our study), the potential for improvement has not been exploited. Although they were offered targeted therapy for upper limb function (robot-assisted therapy (1), Constraint-Induced Therapy Versus Bilateral Arm Training (4)) that resulted in improvement, we are unable to compare the outcomes as the authors used different clinical tests than we did. Their therapy (1, 4) did not affect self-sufficiency and probably not the degree of neurologic disability (which, unfortunately, we cannot compare).

In our opinion, the timeliness of therapy plays a major role in the possibility of recovery. This is possibly due to the appropriate timing of complex intensive rehabilitation into the sub-acute phase (16–18, 30) when spontaneous processes (3, 19–21) leading to recovery can be suitably enhanced (6, 22).

Since in our study we do not evaluate the effect of any targeted therapy on the function of the upper limbs, we can attribute their improvement to the complexity and intensity of the rehabilitation.

Among the strengths of our study is the use of validated outcome measures, a high completion rate among participants, and a relatively high number of participants—our sample matches (4, 23, 48, 49) or even exceeds (1, 15, 50) the studies dedicated to this issue.

Among its weaknesses is missing FIM, measuring self-efficiency, in the control group. As secondary outcomes, parameters related to neurological deficits were chosen. However, the analyses showed that the FIM score in the control group would be useful for comparing the difference in therapy effect between groups.

Despite the limitations of the current study, we believe it provides valuable resource for future research. In this study, we described impaired muscle strength and dexterity in individuals with stroke in comparison to controls. We showed that muscle strength and dexterity may affect their independence. Furthermore, we found, a very important finding for clinical work, that impaired muscle strength and dexterity can be improved by a comprehensive intensive rehabilitation program (not only by means of specific therapy aimed at improving

the function of the upper limbs, as is often documented in the literature). This program was even associated with lowered neurological disability and improved self-sufficiency. Further studies are needed to study effect of individual physiotherapeutic techniques combined in COMIRESTROKE and to compare its effect with other treatments.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the corresponding author upon request.

Ethics statement

The studies involving humans were approved by the Ethical committee of the Institute for the Clinical and Experimental Medicine and Thomayer University Hospital have approved the study under number 09306/22. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ŘK: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. MP: Conceptualization, Methodology, Software, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. VM: Software, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. MB: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. HJ: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. HD: Investigation, Writing – original draft, Writing – review & editing. ID: Investigation, Writing – original draft, Writing – review & editing. LL: Investigation, Writing – original draft, Writing – review & editing. VR: Investigation, Writing – original draft, Writing – review & editing. ZJ: Investigation, Writing – original draft, Writing – review & editing. BJ: Investigation, Writing – original draft, Writing – review & editing. MV: Conceptualization, Visualization, Writing - review & editing. PT: Investigation, Resources, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effects of fully immersive virtual reality training on cognitive function in patients with mild cognitive impairment: a systematic review and meta-analysis

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Background: Mild cognitive impairment (MCI) is a prodromal stage of dementia. There is no specific medication to slow the progression of MCI. Recent studies have confirmed the positive effects of virtual reality (VR). However, the results are inconsistent due to different types of VR interventions, small sample sizes, and the varying quality of the literature. This study aimed to assess the effects of fully immersive VR on cognitive function in MCI patients.

Methods: A systematic review of published literature was conducted using PubMed, Cochrane Library, Embase, CINAHL, Web of Science, SinoMed, CNKI, Wanfang, and VIP Database. The search period was from inception through March 1, 2024. Eligible studies were randomized controlled trials evaluating the effects of fully immersive virtual reality training on cognitive function in MCI patients. Two investigators independently performed literature screening, data extraction, and quality assessment; a meta-analysis of the included literature was performed using RevMan 5.4. The Cochrane Risk of Bias tool was used to assess the methodological quality.

Results: A total of 11 randomized controlled trials with 525 patients were included. The meta-analysis showed that fully immersive virtual reality training had significant effects on global cognitive function (MD = 2.34, 95% CI [0.55, 4.12], $p = 0.01$); (MD = 0.93, 95% CI [0.30, 1.56], $p < 0.01$), executive function (SMD = -0.60, 95% CI [−0.84, −0.35], $p < 0.01$), and attention (MD = 0.69, 95% CI [0.15, 1.23], $p = 0.01$). Still, the difference in memory (SMD = 0.27, 95% CI [−0.24, 0.78], $p = 0.30$) was not statistically significant. Subgroup analyses showed that executive function could be improved only when the intervention duration was ≥40 h. In contrast, excessive training (≥30 times) was counterproductive.

Conclusion: Fully immersive virtual reality training improved cognitive functioning, executive functioning, and attention in MCI patients but was less effective in improving memory. Subgroup analysis suggests that fully immersive VR training must ensure sufficient intervention duration while avoiding frequent interventions.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, PROSPERO (CRD42024498629).

KEYWORDS

fully immersive virtual reality, mild cognitive impairment, cognitive function, executive function, memory, attention, meta analysis

Introduction

Mild Cognitive Impairment (MCI) is a precursor stage of dementia, and its main symptoms include a decline in cognitive functions such as attention, memory, and executive function. Statistical data indicates that approximately 46% of individuals diagnosed with MCI will subsequently develop dementia within the following 3 years (Jia et al., 2020). Currently, there are no specific drugs that are effective in slowing the progression of MCI. Therefore, early screening of MCI patients and implementation of timely and effective non-pharmacological interventions is an effective way to slow down the progression to dementia (Petersen et al., 2018).

Virtual reality (VR) training is an emerging human-computer interaction technology targeted to create artificial interaction scenarios with multi-sensory, fun, and motivational elements. It can significantly overcome temporal and spatial limitations and is gradually becoming an emerging tool for cognitive training and rehabilitation of patients with MCI (Jang et al., 2023). According to the level of immersion, VR can be categorized into non-immersive, semi-immersive, and fully immersive. Among them, fully immersive VR technology is based on stereoscopic projection, 3D displays, motion capture, and other interactive devices, which are more capable of constructing a real interactive and fully engaged virtual environment than non-immersive or semi-immersive ones (Hsu et al., 2022). Currently, some studies have shown that virtual reality can improve the cognitive function of patients with MCI. However, the different types of VR interventions, the small sample size of the studies, and the variable quality of the literature led to inconsistent elaboration of the findings. It is not possible to accurately determine that virtual reality training is more effective than traditional rehabilitation techniques (Riaz et al., 2021). Furthermore, previous studies have concentrated on non-immersive and semi-immersive VR techniques, and existing meta-analyses have combined different VR intervention types. There is no evidence of the effectiveness of fully immersive and interactive features on cognitive functioning in patients with MCI.

The purpose of this systematic review is to identify and analyze randomized controlled trials of fully immersive virtual reality training on cognitive functioning in patients with MCI in order to assess the effectiveness of fully immersive virtual reality training and to discover the benefits of fully immersive VR with full immersion and interaction features on cognitive functioning in patients with MCI.

Materials and methods

Protocol registration

This systematic review has been registered on the PROSPERO (CRD42024498629).

Data sources and search strategy

This study was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We conducted a comprehensive search for relevant articles from various academic databases. Articles were retrieved from PubMed, Cochrane Library, Embase, CINAHL, Web of Science, SinoMed, China National Knowledge Infrastructure, Wanfang, and VIP Database. The last retrieval date was March 1, 2024, and a combination of subject terms and free terms were used, while important references in the articles were traced back to obtain additional relevant literature. The keywords used were "mild cognitive impairment," "mild cognitive decline," "MCI," "cognitive impairment," "virtual reality," "immersive virtual reality," "virtual environment," "virtual rehabilitation," "virtual game," "virtual reality training." The Chinese database used the Chinese translation of the above keywords. Taking PubMed as an example, the specific search strategy is as follows.

#1 Search: "Cognitive Dysfunction"[Mesh]
#2 Search: (mild cognitive impairment [Title/Abstract]) OR (mild cognitive decline [Title/Abstract]) OR (MCI [Title/Abstract]) OR (cognitive impairment [Title/Abstract]) OR (cognitive dysfunction [Title/Abstract])
#3 Search: #1 OR #2
#4 Search: "Virtual Reality"[Mesh]
#5 Search: (virtual environment [Title/Abstract]) OR (Virtual Reality [Title/Abstract])) OR (immerse virtual reality [Title/Abstract]) OR (virtual rehabilitation [Title/Abstract])) OR (virtual game [Title/Abstract]) OR (virtual therapy [Title/Abstract])) OR (virtual treatment [Title/Abstract]) OR (VR [Title/Abstract])
#6 Search: #4 OR #5
#7 Search: #3 AND #6

Inclusion and exclusion criteria

The eligibility criteria based on the PICOS (Participant, Intervention, Comparison, Outcome, Study design) framework are as follows. (1) Participant: Patients with mild cognitive impairment. Diagnostic criteria included Mini-mental State Examination (11–26 points) and Montreal Cognitive Assessment (<26 points). (2) Intervention: Studies used fully immersive VR training. (3) Comparison: The control group received no intervention or received traditional conventional therapy, non-immersive, and semi-immersive VR training. (4) Outcome: The primary outcome of this study was cognitive function, evaluated using the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Trail-making Test A/B (TMT-A/B), Digital Span Test (DST), Stroop Color and Word Test (SCWT), Symbol Digit Modalities Test (SDMT), Animal Fluency Test (AFT), Language Testing in Asia (LTA); Digit Breadth Test (DBT). Secondary outcomes were daily living function, evaluated using the Instrumental Activities of Daily Living Scale (IADL). (5) Study design: randomized controlled trial. Exclusion criteria: (1) full text or original data is unavailable; (2) combining other interventions except the fully immersive virtual reality training; (3) conference papers; (4) case reports; (5) articles written in a language other than English or Chinese.

Data extraction

Two researchers trained in evidence-based medicine independently screened the studies based on title, abstract, and full

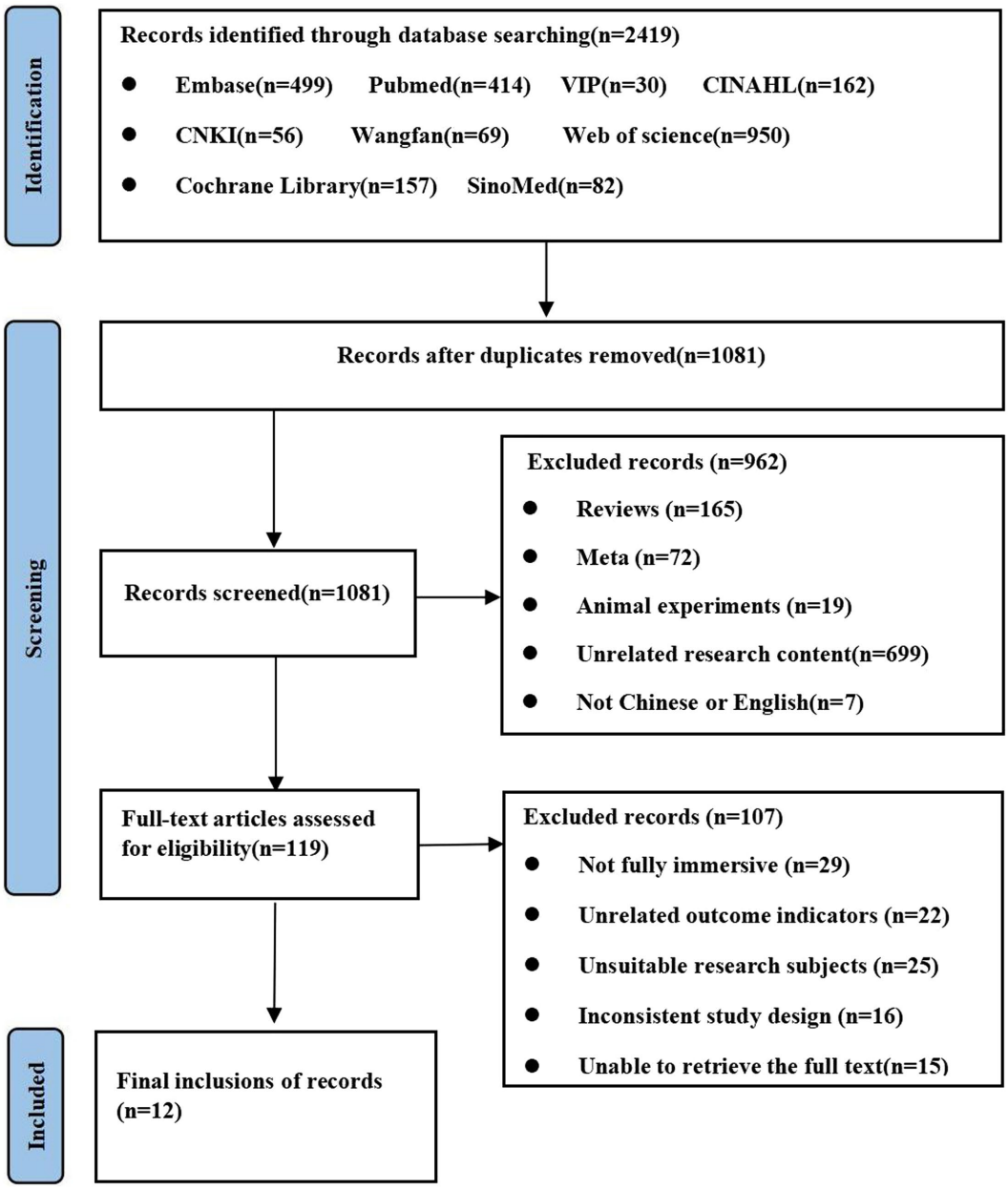

FIGURE 1
Literature screening process and results from each step of the process.

text, then extracted and cross-checked data. In case of disagreement, a third researcher intervened to reach a consensus. The study was based on the Cochrane Handbook 5.1.0 for original data extraction (Higgins et al., 2011), which consisted of three categories: literature characteristics, study participant characteristics, and intervention plan. Literature characteristics included first author, year of publication, and country. Study participant characteristics included age, sample size, and diagnostic criteria. The intervention plan includes test and control group interventions, platforms and tasks for fully immersive virtual reality training, intervention frequency, intervention period, intervention duration, outcome indicators, and measurement tools.

Quality and risk of bias assessments

Two researchers independently assessed the risk of bias in the included literature according to the risk bias assessment tool recommended in the Cochrane Handbook for Systematic Reviews. If there was a disagreement, a third researcher was asked to make a joint decision. The assessment included seven items: (1) generation of randomized sequences, (2) allocation concealment, (3) blinding of subjects and investigators, (4) blinding of outcome assessors, (5) completeness of results and loss of visits, (6) selective reporting, (6) other biases (baseline imbalance, conflict of interest). The evaluation results included "low risk of bias," "high risk of bias," and "unclear."

TABLE 1 Characteristics of included studies.

Studies	Participate		Intervention		Frequency	Duration	Outcome
	Mean age (Mean ± SD)	Sample size (IG/CG)	IG	CG			
Liao et al. (2019)	75.5 ± 5.2/73.1 ± 6.8	18/16	Take the MRT, kitchen chef, convenience store clerk, Tai Chi, football (running and stepping)	traditional cognitive and physical training	60 min/times, three times/week	12 weeks	③④⑤
Park et al. (2020)	71.80 ± 6.61/69.45 ± 7.45	10/11	Crows and seagulls, automated Teller Machine, fireworks Party, shopping in the mart, fruit Cocktail	blank control	30 min/session, two times/week	12 weeks	①⑤⑨
Liao et al. (2020)	75.5 ± 5.2/73.1 ± 6.8	18/16	Taking the MRT, tai chi, looking for a store, stepping and running, kitchen chef, convenience store clerk	traditional cognitive and physical training	60 min/session, three times/week	12 weeks	②⑧⑩
Optale et al. (2010)	78.5 ± 10.9/81.9 ± 5.0	15/16	Noticing the path of a seagull's flight view, leading the way to a destination, listening to training	musical training	Initial training: 30 min/repetition, three times/week. Intensive training:30 min/ session, two times/ week.	12 weeks	①③④⑨⑩
Thapa et al. (2020)	72.6 ± 5.4/72.7 ± 5.6	33/33	Making juice, shooting crows, finding fireworks, correctly placing items	general health promotion	100 min/times, three times/week	8 weeks	①③④⑥
Baldimtsi et al. (2023)	66.07 ± 10.04/74.36 ± 7.04	28/28	Complete 20 simple numerical calculations and memorize the animals in the forest while riding your bike.	blank control	20 min/first 5 sessions, follow-up 30 min/session, 2–3 sessions/ week	12 weeks	①④
Park (2022)	71.93 ± 3.11/72.04 ± 2.42	28/28	Program developed based on Unity game engine to perform the task of finding gems	traditional education and training	45 min/session, three times/week	8 weeks	⑧
Yang et al. (2022)	72.5 ± 5/72.6 ± 5.6	33/33	Making juice, shooting crows, finding fireworks, correctly placing items	health Seminar	100 min/times, three times/week	8 weeks	①③④⑥
Sun et al. (2024)	77.18 ± 6.41/78.03 ± 5.95	32/31	Ba Duan Jin training, supermarket shopping, wing flying, magic tricks, gym, space gravity ball	routine nursing services and health promotion	45 min/times, three times/week	24 weeks	②③④⑦⑨
Wang and Lu (2016)	59.61 ± 8.73	30/30	3D Differential Time Ranging Motion Capture Instrument Captures Patient's 3D Motion Trajectory for Human-Computer Interaction to Complete ADL Training	routine acupuncture points	leave the needle for 40 min/times, during which the needle is rowed once every 10 min.		①②
Luo et al. (2022)	71.31 ± 6.74/74.19 ± 4.69	16/16	Fruit cutting task, obstacle course running task, picture matching task, jigsaw puzzle task, sorting training	routine rehabilitation training	30 min/session, five sessions/week	4 weeks	②③④⑨
Li (2023)	63.61 ± 2.33/65.40 ± 3.15	20/20	Basketball, obstacle track, picture matching, ATM withdrawal, trash sorting, object naming, maze game	routine cognitive training	30 min/session, five sessions/week	4 weeks	②

The outcome indicators were measured with the following instruments: Overall cognitive function ① Mini-Mental State Examination (MMSE); ② Montreal Cognitive Assessment (MoCA). Executive Function: ③ Trail-Making Test A (TMT-A); ④ Trail-Making Test B (TMT-B); ⑤ Stroop Color and Word Test (SCWT); ⑥ Symbol Digit Modalities Test (SDMT). Memory: ⑦ Animal Fluency Test (AFT); ⑧ Language Testing in Asia (LTA). Attention: ⑨ Digit Breadth Test (DBT). Daily living ability: ⑩ Instrumental Activities of Daily Living Scale (IADL).

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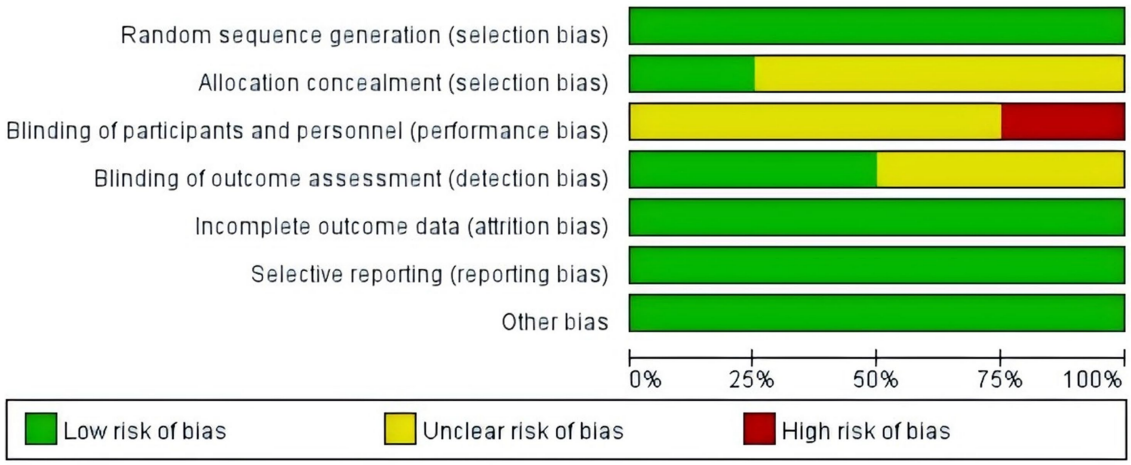

FIGURE 2
Risk of bias graph.

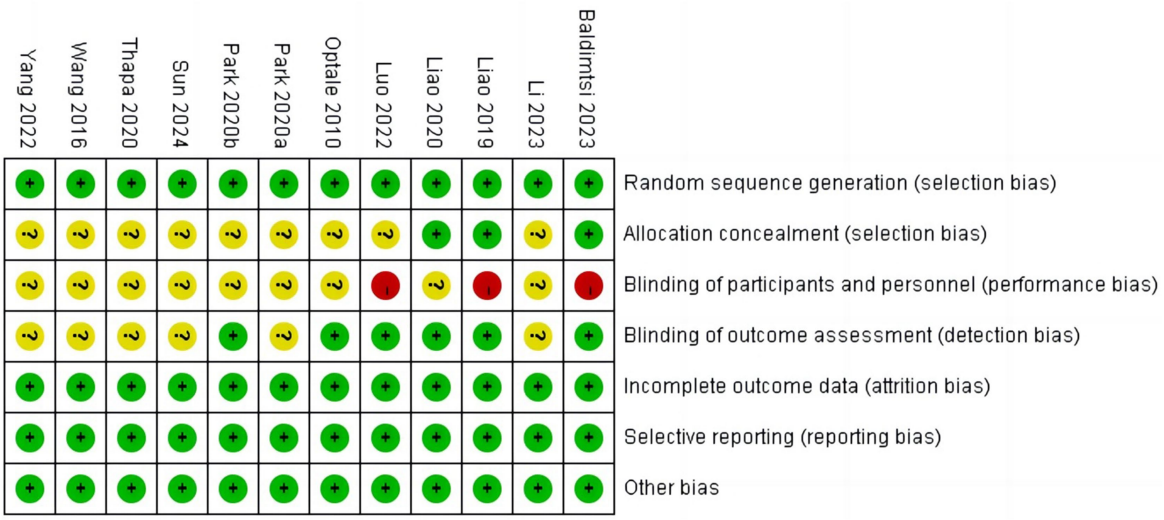

FIGURE 3
Literature quality and publication bias risk assessment.

"Low" indicates that the risk of bias is low, "high" indicates that the risk of bias is high, and "unclear" indicates that the literature does not provide sufficient information for bias analysis.

Data synthesis and analysis

We used the statistical software RevMan 5.4 to analyze the extracted scale data in combination with effect sizes. Considering that the outcome indicators were continuous data, mean difference (MD) or standardized mean difference (SMD) was used as the effect statistic. When the measurement methods and units are the same, MD is selected; otherwise, SMD is selected. Heterogeneity was judged by χ^2 test and I^2 statistic; if $p > 0.1$, $I^2 \leq 50\%$, a fixed effect model was chosen; if $p \leq 0.1$, $I^2 > 50\%$, the source of heterogeneity was judged by subgroup analysis and sensitivity analysis, if still not able to exclude apparent clinical heterogeneity, a random effect model was chosen. This study calculated a 95% confidence interval (95% CI), and $p < 0.05$ was considered statistically significant. In addition, if the number of studies was ≥4, funnel plot analysis was used to detect publication bias.

Results

Description of included studies

The included 12 studies, consisting of 11 RCTs, involved a total of 525 participants. The specific selection process is shown

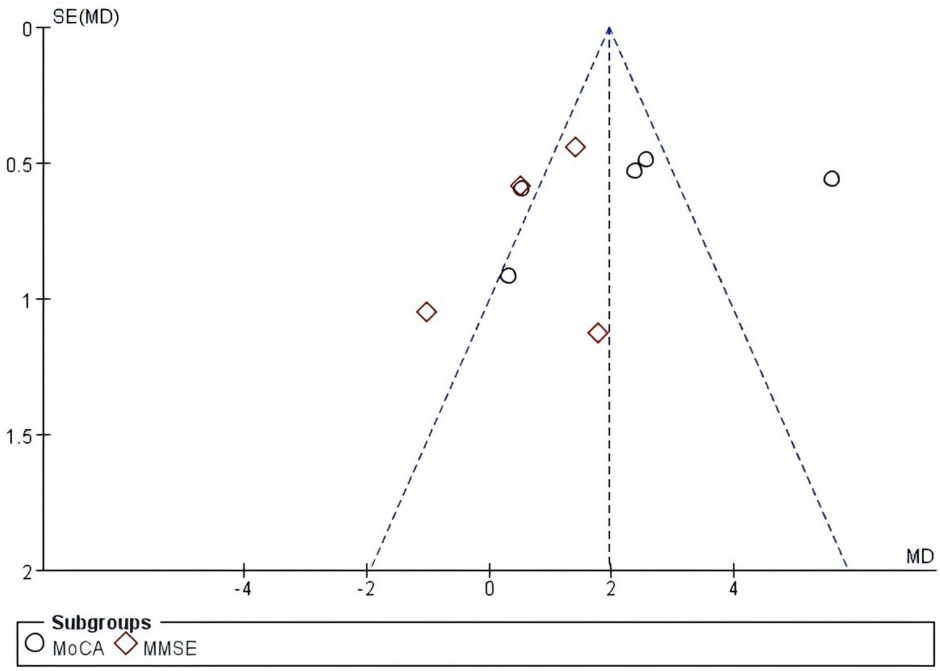

FIGURE 4
Funnel plot of the global cognitive function.

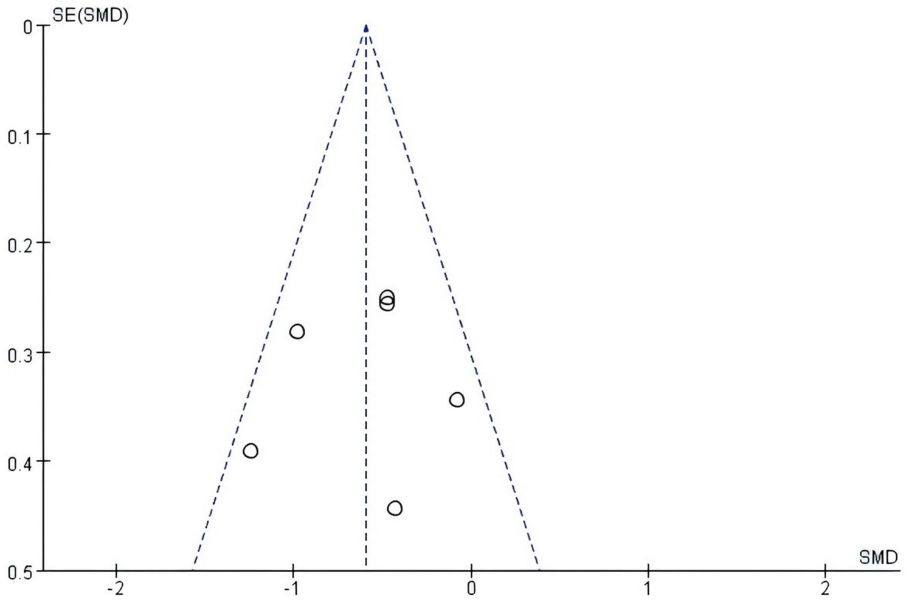

FIGURE 5
Funnel plot of executive function.

in Figure 1. Among the studies, there was a considerable difference in sample size, ranging from 21 to 66. The total duration of the training was from 12 to 60 h, and the total number of training sessions ranged from 20 to 72. More detailed information on the characteristics of the included studies is presented in Table 1.

Literature quality and publication bias risk

Results of the literature quality and publication bias risk assessment are presented in Figures 2, 3. Sensitivity analysis was also performed on the included outcome indicators, and after excluding each literature one by one, there was no effect on the intervention

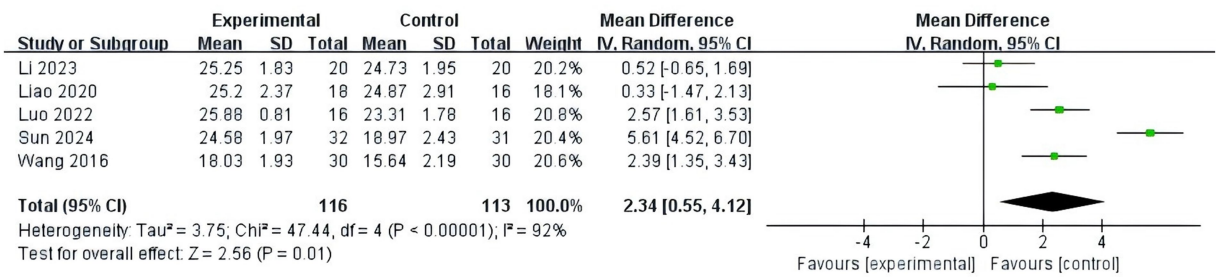

FIGURE 6
Meta-analysis results of global cognitive function (MoCA).

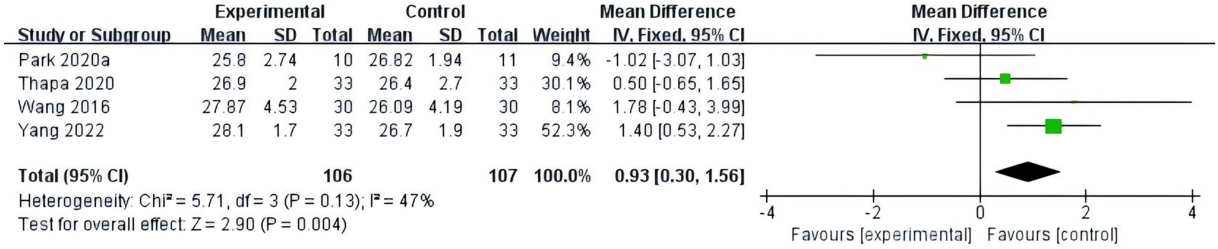

FIGURE 7
Meta-analysis results of global cognitive function (MMSE).

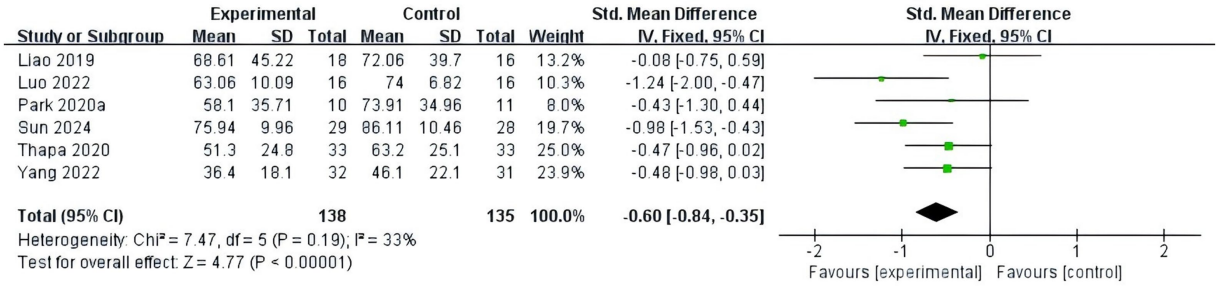

FIGURE 8
Meta-analysis results of executive function.

outcome, suggesting no publication bias. Therefore, the results of this study are reliable.

Publication Bias

Funnel plots were drawn for the overall cognitive function and executive function evaluation indicators, as shown in Figures 4, 5. It was found that there was a low risk of publication bias due to the symmetry of the left and right scatterplots.

Main effects and subgroup analysis

Global cognitive function

Five studies (Wang and Lu, 2016; Liao et al., 2020; Sun et al., 2024; Luo et al., 2022; Li, 2023) used the MoCA scale to compare global cognitive function and included 113 MCI patients with high heterogeneity ($p < 0.01$, $I^2 = 92\%$) among the results. Therefore, a sensitivity analysis was performed using the one-by-one elimination method. After sensitivity analysis, it was found that heterogeneity was not reduced, and a random effects model was used for meta-analysis. The results showed that the MoCA score of the fully immersive VR training was significantly different from the control group (MD = 2.34, 95% CI [0.55, 4.12], $p = 0.01$), as shown in Figure 6.

Four studies (Thapa et al., 2020; Park, 2022; Yang et al., 2022; Wang and Lu, 2016) used the MMSE scale to assess the global cognitive function and included 107 MCI patients with high homogeneity ($p = 0.13$, $I^2 = 47\%$) among the results. Therefore, a fixed-effects model was used for analysis. The results showed that fully immersive VR training was effective in improving the global cognitive function of MCI patients; the difference was statistically significant (MD = 0.93, 95% CI [0.30, 1.56], $p < 0.01$), as shown in Figure 7.

TABLE 2 Subgroup analysis of the effects of fully immersive virtual reality training on executive functions in patients with mild cognitive impairment.

Subgroup	Number	Group (cases)		Heterogeneity		SMD (95%CI)	Meta-analysis results	
		VR	Control	I^2 (%)	p		Z	p
Total period of intervention (weeks)								
<10	3	81	80	37	0.20	−0.61 (−0.92, −0.29)	3.73	<0.01
≥10	3	57	55	53	0.12	−0.58 (−0.97, −0.20)	2.98	<0.01
Total frequency of interventions (times)								
<30	4	91	91	10	0.35	−0.58 (−0.88, −0.29)	3.83	<0.01
≥30	2	47	44	76	0.04	−0.55 (−1.44, 0.33)	1.22	0.22
Total duration of intervention (h)								
<40	3	44	43	60	0.08	−0.57(−1.20, 0.13)	1.59	0.11
≥40	3	94	92	14	0.31	−0.62(−0.92, −0.32)	4.11	<0.01

Executive function

A total of six studies (Liao et al., 2019; Park et al., 2020; Thapa et al., 2020; Yang et al., 2022; Sun et al., 2024; Luo et al., 2022) were included, with TMT-A/B or SCWT as the outcome indicator, so SMD was used for analysis. This study included 135 patients with MCI and showed low heterogeneity ($p = 0.19$, $I^2 = 33\%$). Therefore, a fixed-effects model was used for meta-analysis. The results showed that fully immersive VR training can improve the executive function effectively of MCI patients, and the difference is statistically significant (SMD = -0.60, 95% CI [−0.84, −0.35], $p < 0.01$), as shown in Figure 8. Subgroup analysis was carried out in this study to compare the effects of intervention frequency, intervention period, and total intervention duration, and the results are shown in Table 2.

Memory

Three studies (Liao et al., 2020; Park, 2022; Sun et al., 2024) compared memory using VLT/AFT and included 75 MCI patients with high heterogeneity ($p = 0.08$, $I^2 = 60\%$) among the results. The sensitivity analysis did not reduce heterogeneity. Therefore, a random-effects model was used for meta-analysis. The results did not observe any improvement in memory in MCI patients with fully immersive VR training, and the difference was not statistically significant (SMD = 0.27, 95%CI [−0.24, 0.78], $p = 0.30$), as shown in Figure 9.

Attention

Two studies (Park et al., 2020; Luo et al., 2022) compared attention using the DST and included 27 MCI patients with high homogeneity ($p = 1.00$, $I^2 = 0\%$) among the results. Therefore, a fixed-effects model was used for meta-analysis. The results showed that fully immersive VR cognitive training effectively improved attention in MCI patients, and the difference was statistically significant (MD = 0.69, 95% CI [0.15, 1.23], $p = 0.01$), as shown in Figure 10.

Daily activity ability

Two studies (Liao et al., 2020; Optale et al., 2010) compared daily activity ability using the ADL scale, but the findings were inconsistent. Optale (Optale et al., 2010) noted that the difference in ADL scale scores between the two groups of patients with MCI was not statistically significant for fully immersive VR training. In contrast, Liao (Liao et al., 2020) noted that fully immersive VR training enhanced the ability of daily living of MCI patients. The ADL scores of the experimental group were significantly higher than those of the control group [control group (18.25 ± 2.04), experimental group (19.77 ± 2.12), $p < 0.01$].

Discussion

Patients with MCI are often accompanied by a decline in verbal expression, reduced ability to adapt to the environment, and decreased spatial awareness, which can seriously affect their global cognitive function and social adaptability. A significant improvement over control groups was reported in the global cognitive function in fully immersive VR groups, in line with the findings of Wu et al. (2020), Yu et al. (2023), and Yan et al. (2022). The reason may be that fully immersive VR technology provides patients with rich visual, auditory, and tactile stimuli, and the multi-domain task setting enables participants to obtain comprehensive sensory stimulation, which benefits spatial cognition and language function. Analyzed from a neuroanatomical perspective, VR training has been demonstrated to facilitate neuroplastic changes by stimulating brain excitability, promoting synaptic plasticity, and neuronal functional integration in neural networks (Ten Brinke et al., 2019). In addition, based on the cognitive reserve theory, MCI patients can engage in cognitive stimulus-related activities to increase neural reserve to prevent cognitive decline (Vujic et al., 2022). Another study showed that there was no statistically significant improvement in global cognitive functioning with fully immersive VR training, which may be related to the short duration of the intervention and the absence of a dual cognitive and physical training regimen (Park, 2022). Furthermore, some scholars have pointed out that potential confounders such as nutritional status, physical activity, and sleep patterns can also affect study results (Vujic et al., 2022).

Global cognitive functioning in this study was mainly assessed by the MMSE or MoCA or combined effects scales. Several studies have shown that the MoCA scale has higher sensitivity and specificity than the MMSE scale in assessing the cognitive function of MCI patients, which may explain the difference between the MMSE and MoCA scores in the study of Ding (Yan et al., 2021; Scott and Mayo, 2018; Ding, 2023). This study found that both the MMSE and MoCA scores

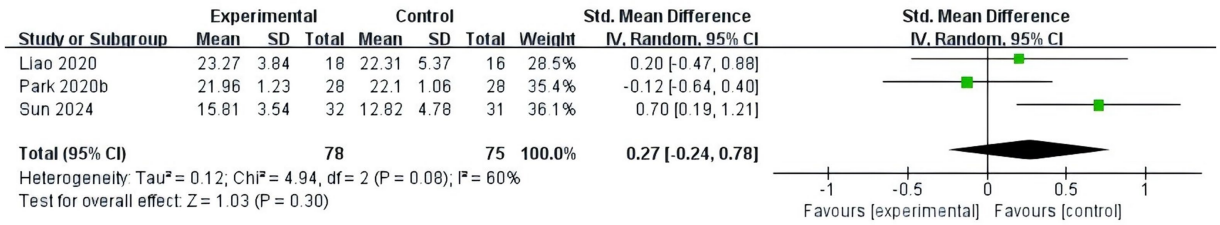

FIGURE 9
Meta-analysis results of memory.

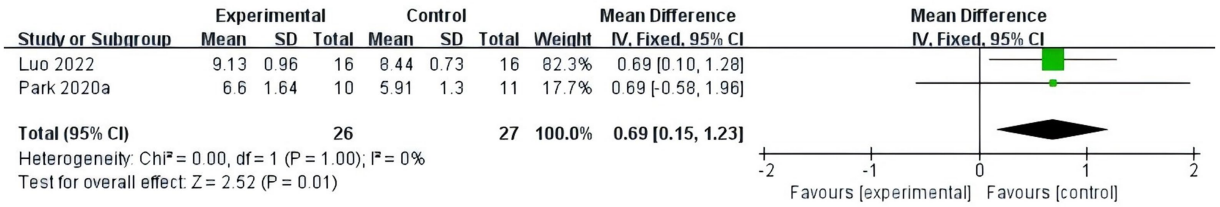

FIGURE 10
Meta-analysis results of attention.

in the experimental group showed significant improvement in cognitive function, which was mainly considered as the fact that compared with semi-immersive or non-immersive VR, fully immersive VR training is more conducive to remodeling cognitive functions by allowing the patients to immerse themselves in virtual environments and extend the training results to real life, as well as realizing the task-oriented and repetitive high-intensity training.

Executive functioning involves a variety of skills such as working memory, inhibitory control, and cognitive flexibility, which are required to cooperate with brain processing to accomplish higher-order tasks. Meta-analysis of this study showed that fully immersive VR training could help to improve the executive function of MCI patients. This may be attributed to the fact that the fully immersive VR technology provided diverse game scenarios and tasks, which further differentiated the training goals of MCI patients and clarified the purposefulness of the rehabilitation. Additionally, the plasticity of the executive function was enhanced, leading to an increase in the patient's executive function and stabilization of the patient's clinical status. From a neuroanatomical perspective, virtual reality training scenarios are characterized by high levels of visual realism, which has been shown to enhance the production of brain-derived neurotrophic factor (BDNF) and improve the capacity to store and process information.

Subgroup analyses revealed that a significant improvement in executive function was observed only when the duration of intervention was 40 h or more. Conversely, excessive training frequency (30 times or more) had a detrimental effect on the intervention outcome. The reasons for these findings are twofold: First, executive function involves a range of higher-order cognitive functions, making it more challenging to improve and necessitating complex cognitive training. Therefore, a more extended intervention duration may lead to improved executive function. Second, fully immersive VR training environments possess strong closure, high fidelity, and complete immersion. However, frequent exposure to such an environment for a fixed period may lead to fear, boredom, and resistance in patients with MCI, affecting their motivation and training efficiency. Additionally, another study found no statistically significant improvement in executive function with fully immersive VR training compared to conventional treatment (Park, 2022). This could be attributed to the short intervention time and the need for consideration for intervention frequency and other follow-up data. These findings underscore the importance of ensuring sufficient intervention time and period in future research while also avoiding overly frequent training, which can compromise the effectiveness of the intervention.

Attention is necessary for individuals to allocate cognitive resources and maintain task processing while performing tasks (Yang et al., 2022). Fully immersive VR training improves attention in patients with MCI mainly because patients receive multimodal visual and auditory stimuli as well as complete functional reality tasks in fully immersive virtual scenarios, which significantly enhances the continuous integration of practical perceptual and attentional stimulation aspects. Currently, the strategy of fully immersive virtual reality training focuses on complex modules such as educational games and supermarket shopping, with less emphasis on attention training. It is worth noting that attention is the basis of other cognitive functions. Patients with attention deficits have difficulty focusing on the training process, resulting in poor improvement in cognitive function. Therefore, it is recommended that medical staff appropriately increase attention training sessions to comprehensively promote the recovery of patient's cognitive function.

Memory is comprised of both short-term and long-term memory processes, and the decline in memory function is most pronounced during the cognitive decline observed in patients with MCI. The limited effect of fully immersive VR training in improving memory remains consistent with the findings of Wu (Wu et al., 2020) and Yu (Yu et al., 2023). The rationale for this conclusion was that only two papers were included in the study, and false-negative results may have

occurred due to the limited number of documents. Furthermore, it has been suggested that potential confounding variables, such as nutritional status, physical activity, and sleep patterns, may also influence the intervention effect (Ding, 2023). In the future, the effects of fully immersive virtual training on memory function can be further studied by incorporating more research and increasing the duration of the intervention.

The ability of daily living requires complex cognitive processing, involving working memory, attention, processing speed, and other cognitive domains (Luo et al., 2022) Therefore, this study considers that abilities of daily living must be taken into account when assessing cognitive function. At present, there are fewer original studies on the ability of daily life of MCI patients through fully immersive VR training, and the results need to be further examined. Liao found that fully immersive VR training enhanced the ability of daily life activities of MCI patients, and the reason for this is considered to be the fact that fully immersive VR achieves more precision and completeness in daily life training through multi-module training of memory and executive function (Liao et al., 2020). It is worth mentioning that enhancing daily living ability is a complex integration process. It is not the case that improvement in a single cognitive domain can improve the ability to live life, which explains why there is difference in ADL scale scores between the two groups of MCI patients is not statistically significant in the study by Optale (Optale et al., 2010). However, although the effect of the intervention needs to be further verified, it cannot be ignored that fully immersive VR training brings positive feedback from visual, auditory, and other proprioceptive senses through personalized rehabilitation, ultimately improving patient engagement and motivation.

In conclusion, fully immersive virtual reality training improves global cognitive function, executive function, and attention in patients with MCI. However, several limitations to this study must be addressed. First, the results of this meta-analysis were limited to fully immersive virtual reality training, while the type of study was restricted to RCTs, so future studies with larger sample sizes and higher quality are still needed to validate the above findings further. Second, the quality of the included studies was not high, and the risk of bias in some studies was unclear, so the conclusions may need to be treated with more caution when applied to clinical practice. Third, only Chinese and English literature was included, which may have resulted in the omission of high-quality literature in other languages. Therefore, it is recommended that future studies include more databases and languages for retrieval to improve the reliability of the research.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JY: Data curation, Methodology, Writing – original draft. JS: Methodology, Writing – review & editing. QS: Data curation, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Global research hotspots and trends of theta burst stimulation from 2004 to 2023: a bibliometric analysis

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Background: Theta burst stimulation (TBS) has garnered widespread attention in the scientific community, but a comprehensive bibliometric analysis of TBS research remains absent. This study aims to fill this gap by elucidating the characteristics, hotspots, and trends in TBS publications over the past 20 years using bibliometric methods.

Methods: We retrieved TBS-related publications from January 1, 2004, to December 31, 2023, from the Web of Science Core Collection (WoSCC). The analysis focused on articles and review articles. Data were processed using the bibliometric package in R software, and CiteSpace and VOSviewer were employed for bibliometric and knowledge mapping analyses.

Results: A total of 1,206 publications were identified, with 858 included in the analysis. The annual publication volume showed a fluctuating upward trend. Leading institutions and authors were predominantly from the United States of America (USA) and European countries. Core journals and publications also primarily originated from these regions. Current research hotspots include the clinical applications and mechanisms of TBS in neurorehabilitation and depression. TBS cerebellar stimulation has emerged as a promising therapeutic target. Future research is likely to focus on dysphagia, cognitive impairments, and post-traumatic stress disorder.

Conclusion: This bibliometric analysis provides an overview of the basic knowledge structure, research hotspots, and development trends in TBS research over the past two decades. The findings offer valuable insights into the evolving landscape of TBS research and its potential directions.

KEYWORDS

theta burst stimulation, bibliometric analysis, hotspots and trends, VOSviewer, CiteSpace

1 Introduction

Endogenous theta frequency oscillations in hippocampal and cortical circuits are critical for learning, motor function, and memory processing (1). Theta burst stimulation (TBS) mimics this natural electrophysiological activity, providing a unique non-invasive neural stimulation method (2). The most commonly used TBS paradigms include intermittent TBS

(iTBS) and continuous TBS (cTBS), each modulating cortical excitability through distinct stimulation patterns. The iTBS protocol consists of 2 s of continuous stimulation followed by an 8-s interval, repeated in cycles, and is believed to induce long-term potentiation (LTP) (3). In contrast, cTBS involves uninterrupted bursts of stimulation at a fixed frequency for 40 to 50 s, which is thought to induce long-term depression (LTD) (4). LTP and LTD are fundamental concepts in synaptic plasticity, considered key mechanisms underlying learning and memory. However, the manifestation and functional role of these mechanisms in the human brain remain contentious, as most human studies on LTP and LTD are extrapolated from animal models (5, 6). Some research suggests that other forms of synaptic plasticity, such as short-term plasticity and synaptic normalization mechanisms, may also play significant roles in learning and memory, potentially interacting with LTP and LTD in a collaborative manner (7). As a form of patterned repetitive transcranial magnetic stimulation (rTMS), TBS offers several advantages over traditional rTMS, including shorter stimulation times, lower intensity, longer-lasting effects, and a stimulation pattern that more closely resembles natural neural activity (8). These characteristics not only enhance the safety and comfort of TBS but also improve its specificity and efficacy in modulating neural network functions (9). Therefore, TBS holds significant potential in both basic neuroscience research and clinical applications, providing new perspectives on the regulation of brain function (10–13).

Despite extensive research into TBS, its diverse and complex research directions present challenges for newcomers and researchers in the field. Bibliometrics, an interdisciplinary field that applies mathematical and statistical methods to analyze written communication, can provide valuable insights into the quantitative aspects of literature, including publication volume, citation impact, and spatial distribution. This method reveals the development status and trends within a field, helping to identify academic frontiers, hotspots, and evolving research themes (14). Bibliometric analysis has widespread applications in academic research, discipline development, scientific evaluation, and information services (15, 16). However, to date, no comprehensive bibliometric analysis has been conducted specifically on TBS research. The systematic knowledge structure, evolutionary paths, and research hotspots in this field remain underexplored. This study aims to fill this gap by using bibliometric methods to analyze TBS-related publications from the Web of Science Core Collection (WoSCC) over the past 20 years. Our goal is to visually present the research framework, identify key trends, and explore the evolving hotspots in TBS research, thereby offering valuable insights for future investigations in this rapidly developing field.

2 Materials and methods

2.1 Data sources and search strategy

Given that the Web of Science Core Collection (WoSCC) and Scopus are widely recognized as the leading bibliometric databases, other databases that do not provide co-citation data significantly limit the scope and depth of bibliometric analyses (17). Although Scopus is a comprehensive resource, it includes a substantial number of articles without impact factors, which may introduce a degree of uncertainty regarding the reliability of the analytical results (18). To ensure a robust and systematic analysis, this study utilized the WoSCC. The WoSCC encompasses the following sub-databases: the Science Citation Index Expanded (SCI-EXPANDED), the Social Sciences Citation Index (SSCI), the Arts & Humanities Citation Index (A&HCI), the Conference Proceedings Citation Index—Science (CPCI-S), the Emerging Sources Citation Index (ESCI), the Current Chemical Reactions Index (CCR-EXPANDED), and the Index Chemicus (IC). A title-based search was conducted on June 1, 2024, using the query: TI = ("theta burst stimulation") OR ("iTBS") OR ("cTBS") to identify relevant publications from January 1, 2004, to December 31, 2023. Given the relatively limited number of publications in the field of TBS prior to 2004, this timeframe was deemed appropriate to represent the current state of research in this area. The inclusion criteria were restricted to articles and reviews published in English. Following independent searches conducted by two researchers, and subsequent cross-verification, non-relevant publications—such as letters, newspapers, conference papers, and news articles—that did not meet the inclusion criteria were excluded. Duplicate records were also removed. Ultimately, a total of 858 publications were included in the analysis. Relevant documents were exported in TXT format, which included full-text records and references. These data were then imported into bibliometric analysis software for subsequent visualization. The study workflow is illustrated in Figure 1.

2.2 Data processing and analysis

For the comprehensive quantitative analysis of publication volume, countries, institutions, authors, journals, references, and keywords, we employed CiteSpace (version 6.1.R3 Advanced), VOSviewer (version 1.6.20), and the R-bibliometrix package (version 4.3.2) (19) (detailed variable analysis is provided in Supplementary material S1). Prior to the analysis, several preprocessing steps were implemented to ensure data quality. These steps included the normalization of synonyms, removal of irrelevant terms, and standardization of variations in author and institutional names (specific preprocessing details are provided in Supplementary material S2). Using CiteSpace, we extracted detailed information from the data, including collaboration networks among countries and institutions, trends in disciplinary development, citation and co-citation analyses, and the identification of emerging research trends (20) (see Supplementary material S3 for detailed visual interpretations). VOSviewer facilitated the extraction and visualization of key insights from the publication data, particularly through the construction of co-occurrence networks of keywords, which revealed the structure and dynamics of scientific research (21). R-bibliometrix, an open-source tool within the R environment, generated various visual outputs, such as cooperation and trend graphs, thereby enabling the intuitive presentation of the analytical results (22). By integrating the functionalities of these tools, we produced co-occurrence, clustering, and highlighting maps that provide a multi-dimensional view of the TBS field, thereby supporting corresponding analyses.

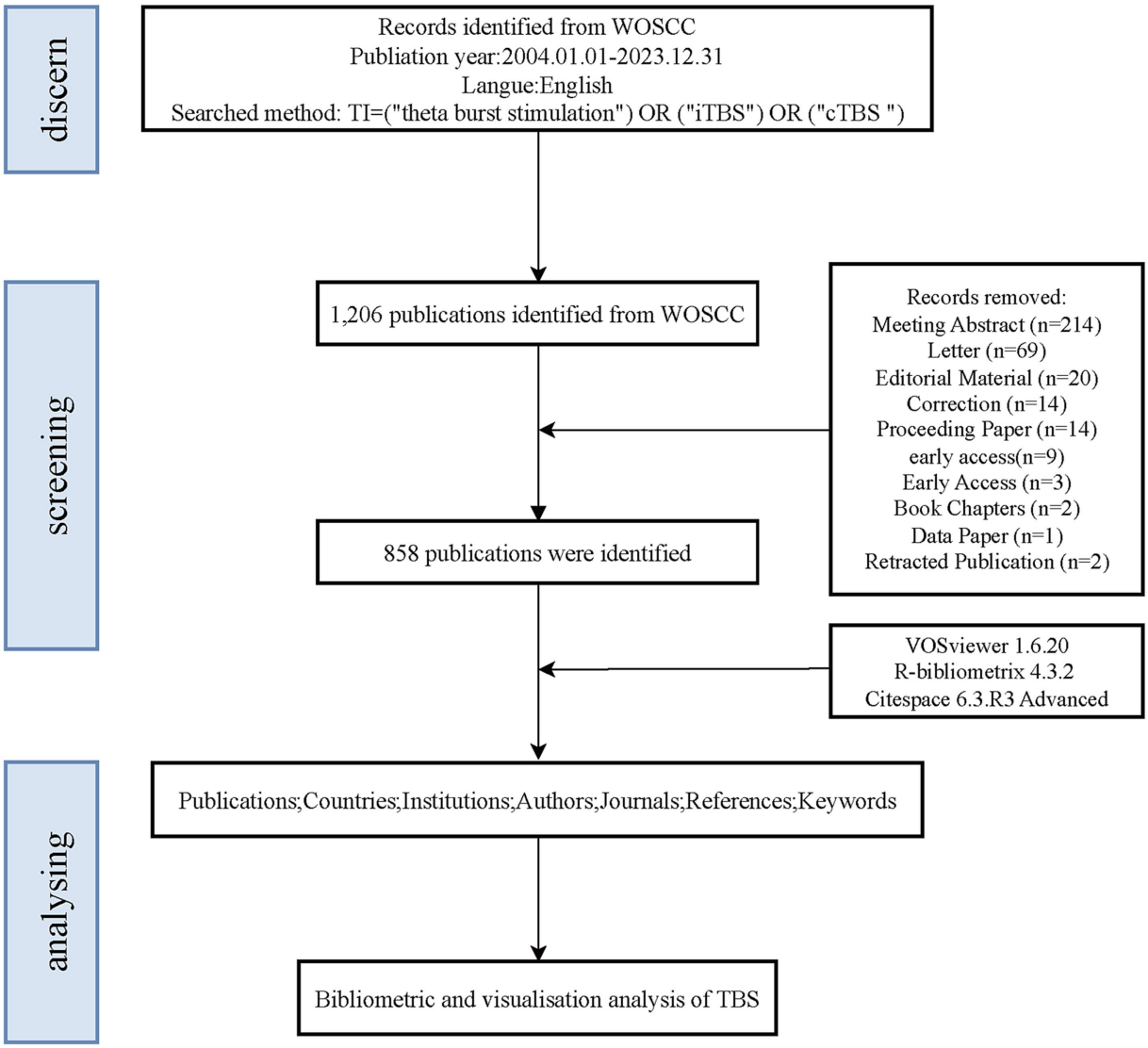

FIGURE 1
Selection and bibliometric analysis workflow of TBS-related research publications.

3 Results

3.1 Annual publication and citation growth trend

Based on the research strategy outlined, a total of 858 publications related to TBS were retrieved from the WoSCC database for the period 2004–2023. The annual number of publications (Np), the average citations per article (ACI), and the Hirsch index (*H*-index) are presented in Figure 2. No related publications were recorded in 2004. From 2005 to 2009, the number of publications grew slowly and steadily, with a slight stagnation observed in 2010, followed by a rapid increase after 2018. The *H*-index of publications from 2004 to 2010 gradually increased, remained stable from 2010 to 2018, and declined post-2019 due to time constraints. The ACI was relatively high between 2005 and 2008, with the highest value observed in 2005.

3.2 Analysis of countries/regions

A total of 57 countries/regions have contributed to TBS-related research. Statistics for the top 10 countries/regions, based on the number of TBS publications, are presented in Table 1. The USA (Np: 180) and China (Np: 161) are the leading contributors, followed by Germany, Canada, and other regions with fewer than 100 publications each. Notably, while the USA and China together account for nearly 40% of the publications in the TBS field, the number of citations (Nc) for the USA was 4,066, which is 2.7 times greater than that of China (Nc: 1,499). The USA also exhibited the highest betweenness centrality (Bc: 0.6), indicating its dominant influence in terms of both the quantity and quality of publications in this field. In the country co-occurrence map (Figure 3A), purple circular nodes represent countries with high Bc (≥0.1). The top five countries by Bc are the USA, the United Kingdom (UK), Germany, Australia, and Canada. Figure 3B illustrates the strong international collaboration, with the

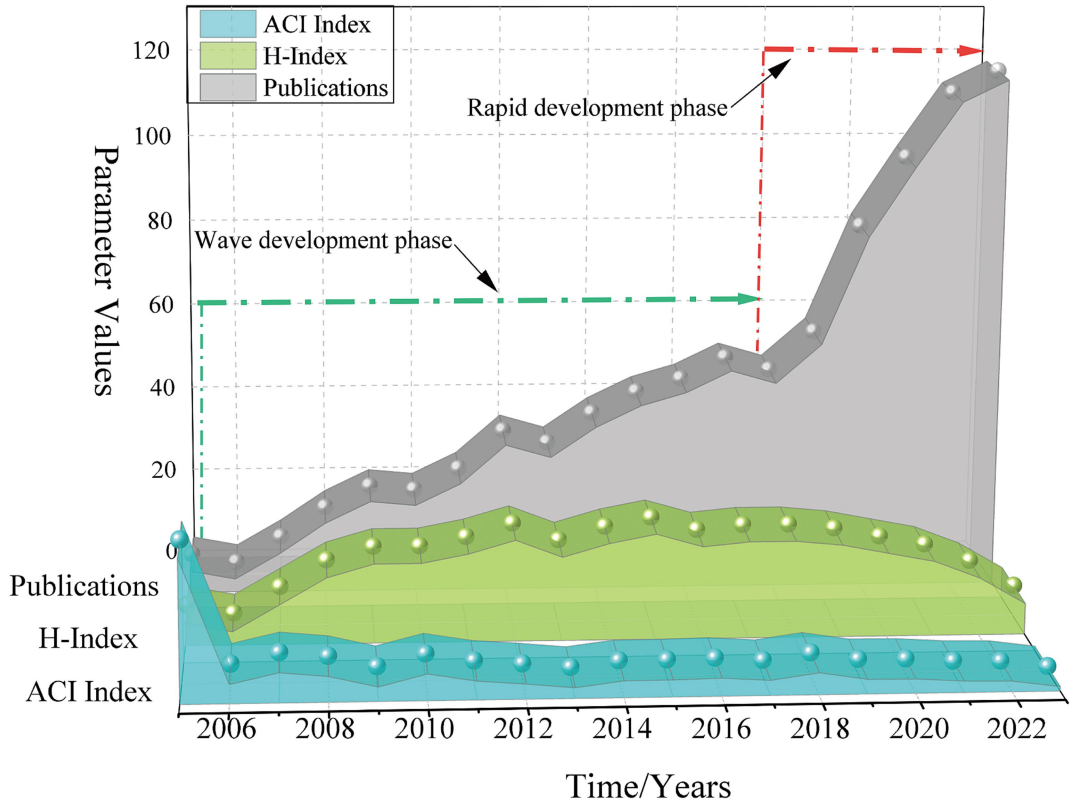

FIGURE 2
Evolution trend of the quantity and citation of publications related to TBS research.

TABLE 1 The top 10 countries/regions by production of TBS-related publications (WoS).

Rank	Country/region	Np	Bc	Nc	*H*-index	ACI
1	USA	180	0.60	4,066	34	22.59
2	China	161	0.01	1,499	21	9.31
3	Germany	105	0.18	3,531	33	33.63
4	Canada	102	0.15	2,803	27	27.48
5	UK	99	0.24	8,114	41	81.96
6	Italy	89	0.14	3,844	35	43.19
7	Australia	68	0.16	2,410	29	35.44
8	Taiwan	56	0.04	5,249	24	93.73
9	Switzerland	42	0.01	1,341	22	31.93
10	Netherlands	37	0.10	875	17	23.65

most frequent partnerships occurring between the USA and the UK, followed by collaborations between the USA and Germany.

3.3 Analysis of institutions

Figure 4A presents the co-occurrence network of major research institutions, with detailed information on the top 10 institutions by publication volume shown in Table 2. Figure 4B displays a Nightingale rose chart representing the overall publication volume. In terms of the number of publications, the University of London (UK) contributed the most (Np: 54), followed by the University of Toronto (Canada) with 46 publications and the Centre for Addiction and Mental Health (Canada) with 33 publications. In terms of Bc, the University of London, the University of California, and Harvard University (USA) ranked in the top three. Institutions with high Bc demonstrate close collaboration, indicating a strong scientific capability in TBS research.

3.4 Analysis of authors

Price's Law was applied to calculate the minimum publication volume of core authors using the mathematical model $M \approx 0.749 \times \sqrt{n_{\max}}$, where M represents the minimum number of

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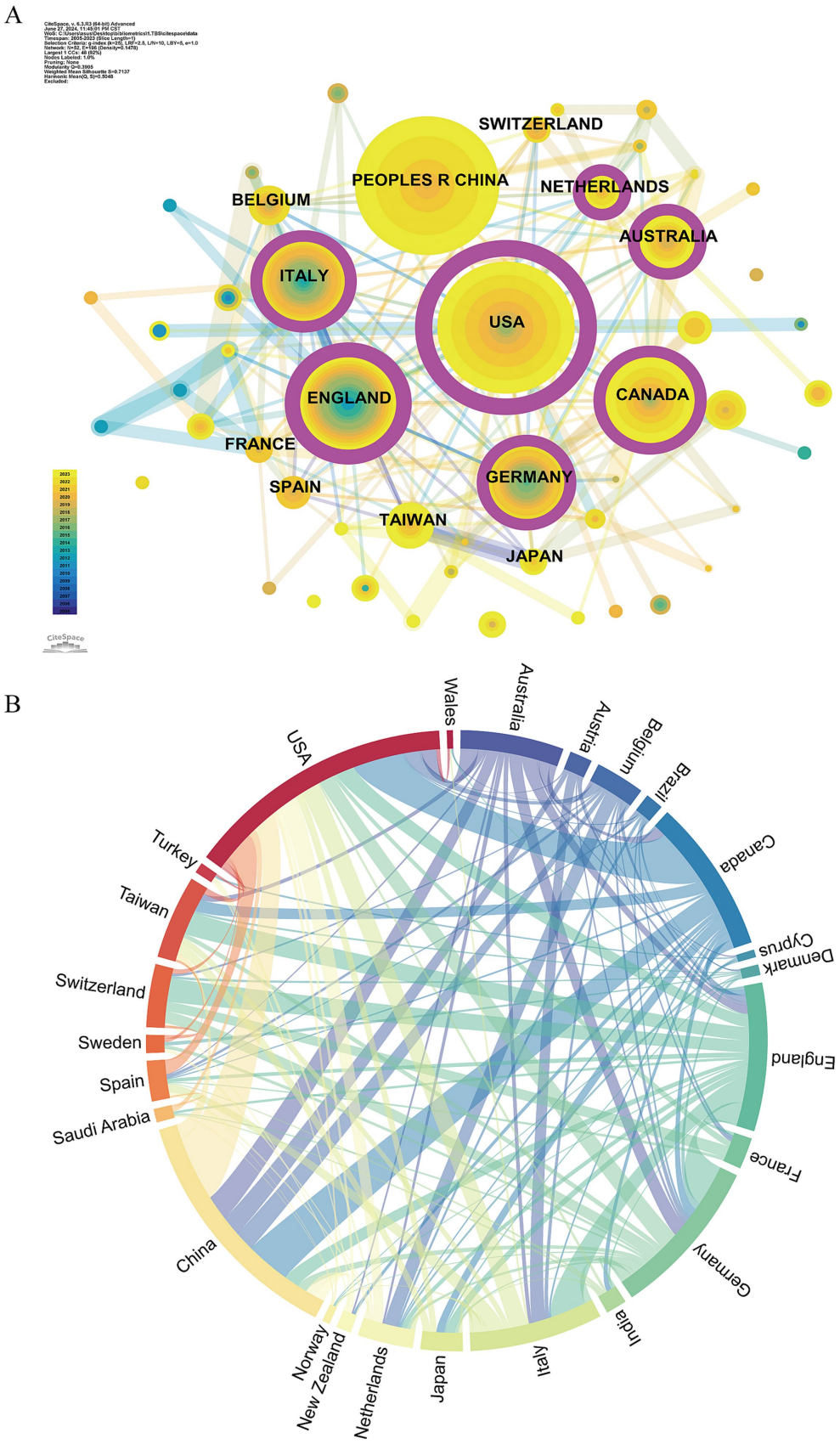

FIGURE 3
The national/regional analysis of TBS-related research. **(A)** The co-occurrence country map of TBS research. Node size indicates co-occurrence frequency, with purple circles representing high Bc (≥0.1). **(B)** The network graph illustrating publication output and collaboration between countries/regions.

publications for core authors, and n_{max} is the highest publication count by a single author. Analysis using CiteSpace software identified $n_{max} = 25$, leading to $M \approx 3.745$. Therefore, authors with four or more publications are classified as core authors, totaling 190 authors (4.96% of all authors). Based on CiteSpace data, a ranking table of the top 10 authors was constructed (Table 3). John C. Rothwell from the Institute of Neurology at University College London leads with 25 publications, followed by Zafiris J. Daskalakis from the University of Toronto and Ying-Zu Huang from Chang Gung University College of Medicine, each with 21 publications. In the co-occurrence network of core authors, most scholars are associated with their own research teams, demonstrating close internal cooperation but a lack of prominent high-Bc authors (Figure 5A). The trend graph of annual publication volumes of high-output authors (Figure 5B) highlights recent active authors in this field, including Zafiris J. Daskalakis, Daniel M. Blumberger, and Chris Baeken. These authors exhibit significant academic vitality, and their research outputs warrant further attention.

3.5 Analysis of journal

During the study period, TBS-related publications appeared in 236 journals. Table 4 shows that the journal with the most publications is *Brain Stimulation* (Np: 54), followed by *Clinical Neurophysiology* (Np: 44), *Frontiers in Neuroscience* (Np: 34), and *Frontiers in Human Neuroscience* (Np: 30). Figure 6A presents a dual-map overlay of journals, visually representing journal distribution, citation patterns, and shifts in research focus. In the TBS field, journals in the categories of molecular biology/immunology and neurology/sports science/ophthalmology frequently cite articles published in journals within the fields of molecular biology/genetics. Figure 6B shows the results of grouping journals according to Bradford's Law, with the core zone (Zone 1) comprising 10 journals, the secondary core zone (Zone 2) consisting of 37 journals, and the non-core zone (Zone 3) containing 186 journals.

3.6 Analysis of reference

Based on Table 5, the top 10 most cited publications on TBS are presented, with the top three each cited over 300 times. The most cited publication is "*Theta Burst Stimulation of the Human Motor Cortex*" by Huang Y. Z. et al., published in *Neuron* in 2005, which has been cited 2,758 times. This pivotal study introduced the definition of TBS, providing a foundation for subsequent research in the field. The second most cited work is "*Effectiveness of Theta Burst* versus *High-Frequency Repetitive Transcranial Magnetic Stimulation in Patients with Depression (THREE-D): A Randomised Non-Inferiority Trial*" by Blumberger D. M. et al., published in *The Lancet* in 2018, with 609 citations. The top 10 references cover a broad spectrum of topics, including neurophysiological mechanisms, clinical applications, and the optimization of TBS protocols.

In Figure 7A, studies with higher Bc predominantly focus on the application and potential of TBS in areas such as neurophysiological and pathological mechanisms, as well as neurosurgical rehabilitation. The cluster analysis of references (Figure 7B) provides an objective view of the knowledge structure in TBS research. The references are categorized into 15 clusters based on the degree of correlation between publications. The largest cluster, #0 focuses on depression, while earlier research clusters include #3 calcium-binding proteins, #8 predictive force control, #11 premotor cortex, and #14 vermis. Subsequent studies have evolved into clusters focused on #0 depression and #2 rehabilitation. In recent years, however, the connectivity between research fields has decreased, with clusters such as #6 post-traumatic stress disorder, #9 transcranial magnetic stimulation combined with electroencephalography (TMS-EEG), #10 auditory feedback, #12 mild cognitive impairment, and #13 dysphagia becoming more independent. These clusters reflect a growing focus on the extension and refinement of TBS applications in clinical disease-related syndromes.

Dependency analysis of the reference clusters, conducted using CiteSpace (Figure 7C), provides a clearer understanding of the current research hotspots and the evolutionary relationships among these clusters. The clusters can be categorized into three main groups: foundational research, bridging clusters, and frontier clusters. Foundational research clusters refer to those that have evolved into other clusters, such as Cluster #11 premotor cortex, Cluster #8 predictive force control, Cluster #1 human, and Cluster #5 spatial attention. Bridging clusters, on the other hand, are those that have both evolved from other clusters and subsequently given rise to additional clusters, serving a connective role in the research process. These include Cluster #3 calcium-binding proteins, Cluster #14 vermis, Cluster #7 cortical excitability, Cluster #2 rehabilitation, and Cluster #0 depression. Among these, Cluster #0 depression stands out with the highest link strength, indicating its significant research prominence. It has evolved from Clusters #14 vermis, #11 premotor cortex, #8 predictive force control, #5 spatial attention, #3 calcium-binding proteins, and #1 human, and further evolved into Clusters #12 mild cognitive impairment, #13 dysphagia, and #10 auditory feedback. A closely related cluster, Cluster #2 rehabilitation, evolved from Clusters #1 human, #3 calcium-binding proteins, #5 spatial attention, and #7 cortical excitability, and subsequently evolved into Clusters #6 post-traumatic stress disorder, #9 TMS-EEG, and #13 dysphagia. Finally, Clusters #6 post-traumatic stress disorder, #9 TMS-EEG, #10 auditory feedback, #12 mild cognitive impairment, and #13 dysphagia have evolved from other clusters but have not yet evolved into additional clusters, suggesting that these topics likely represent the frontier areas of TBS research in recent years.

Figure 7D displays the top 25 references with citation bursts, where the burst duration exceeds 2 years, and the average burst strength is over 9 years, indicating their significant academic contribution. The strongest burst (strength = 36.31) occurred for the groundbreaking 2005 study by Huang Y. Z. et al. In the past 5 years, the study by Blumberger D. M. et al., published in *The Lancet* in 2018, has become highly prominent.

3.7 Analysis of keyword

The keyword density map in Figure 8A highlights the primary research focal points within the TBS field. Prominent terms such as *plasticity*, *depression*, *excitability*, *motor cortex*, *prefrontal cortex*, *efficacy*, and *stroke* frequently appear, each occurring over 80 times with a link strength exceeding 500. These keywords are primarily

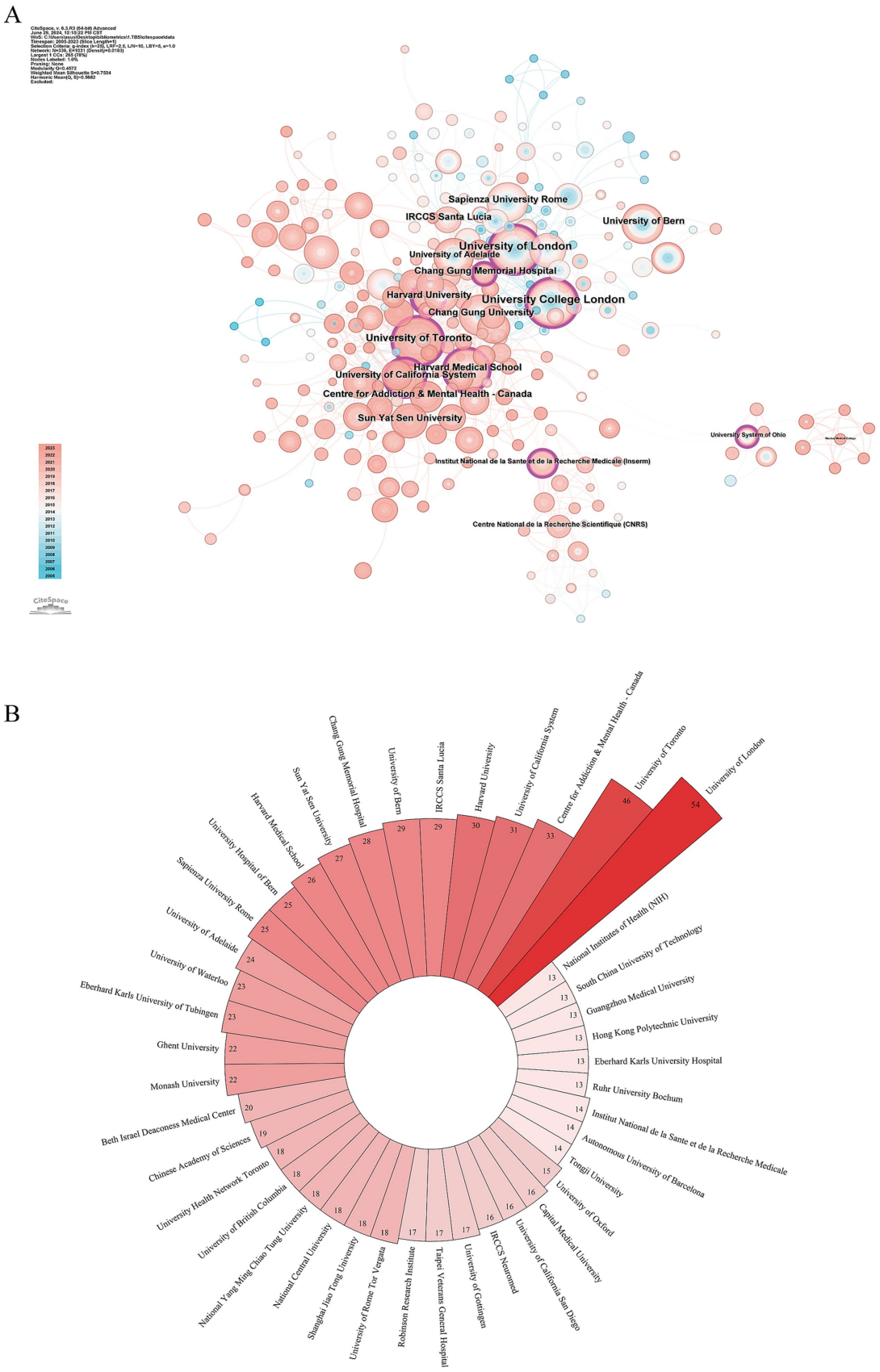

FIGURE 4
The institutional analysis of TBS-related research. **(A)** Co-occurrence institutional map of TBS research. **(B)** South-Nightingale rose diagram showing institutional publication output.

TABLE 2 The top 10 institutions by production of TBS-related publications (WoS).

Rank	Institution	Country/ region	Np	Bc
1	University of London	UK	54	0.19
2	University of Toronto	Canada	46	0.08
3	Centre for Addiction & Mental Health-Canada	Canada	33	0.03
4	University of California	USA	31	0.17
5	Harvard University	USA	30	0.12
6	IRCCS Santa Lucia	Italy	29	0.08
7	University of Bern	Switzerland	29	0.02
8	Chang Gung Memorial Hospital	Taiwan	28	0.07
9	Sun Yat-sen University	China	27	0.07
10	University Hospital of Bern	Switzerland	25	0.01
11	Sapienza University Rome	Italy	25	0.06

TABLE 3 The top 10 authors by production of TBS-related publications (WoS).

Rank	Author	Np	Bc	Nc	ACI
1	Rothwell, John C.	25	0.05	1,704	68.16
2	Daskalakis, Zafiris J.	21	0	283	13.48
3	Huang, Ying-Zu	21	0.01	1,400	66.67
4	Koch, Giacomo	20	0.01	242	12.10
5	Nyffeler, Thomas	19	0	261	13.74
6	Blumberger, Daniel M.	19	0	269	14.16
7	Baeken, Chris	18	0	104	5.78
8	Pascual-leone, Alvaro	18	0.02	236	13.11
9	Ridding, Michael C.	16	0	359	22.44
10	Fitzgerald, Paul B.	16	0	317	19.8

associated with investigations into the neurophysiological mechanisms of TBS and its clinical applications in specific diseases and symptoms.

Figure 8B presents both a cluster map and a timeline view of TBS-related keywords, illustrating the temporal distribution of prominent research topics. Cluster #0 cortical excitability stands out as the largest and most frequently cited research hotspot, having evolved into a major area of focus. Alongside Cluster #0, Clusters #1 plasticity, #2 meta-analysis, #3 dorsolateral prefrontal cortex, #4 speech motor control, #7 magnetic resonance imaging, and #10 ischemic stroke exhibit extended time spans, representing sustained areas of interest in TBS research. In contrast, clusters #5 inhibitory control, #8 intracranial electroencephalography, #9 Parkinson's disease, and #11 activities of daily living have emerged as relatively new areas of investigation. Furthermore, certain keywords, such as cortical excitability and plasticity, have remained consistent throughout the course of research, while others, such as meta-analysis and near-infrared spectroscopy, have only gained significant attention in recent years. Overall, the evolution of these key research terms reflects an initial focus on TBS paradigms and neurophysiological mechanisms, whereas contemporary research has increasingly centered on TBS applications across various diseases and symptoms, as well as an exploration of the central mechanisms involved, particularly within the framework of multimodal diagnostic tools.

4 Discussion

This study employs bibliometric analysis to provide a comprehensive examination of the development and key trends in TBS research, outlining two distinct phases of its progression: the exploratory phase from 2005 to 2018, and the period of rapid growth from 2018 to the present. The analysis investigates several critical metrics, including publication volume, collaboration networks, and citation frequencies, offering a clear view of the global distribution and influence of TBS research. Notably, leading countries, prominent institutions, and key authors have played a pivotal role in shaping the field. However, challenges remain in promoting international collaboration and enhancing academic diversity. Furthermore, the focus of TBS research has gradually shifted from investigating neurophysiological mechanisms to exploring its clinical applications, particularly in neurological rehabilitation and mental health disorders. This bibliometric analysis provides valuable insights into the evolution of TBS research and highlights current research hotspots and emerging trends expected to significantly impact future investigations in the field.

4.1 Current research status

The analysis of annual publication and citation data in TBS research reveals two key developmental phases: the first phase (2005–2018) and the second phase (2018–present). During the first phase, the field experienced initial growth, characterized by fluctuating publication volumes. Although the average annual publication count did not exceed 20 articles between 2005 and 2008, the ACI remained notably high, peaking at 31.65 in 2005. This suggests that early publications had a significant foundational impact, laying the groundwork for subsequent research. Between 2009 and 2018, the publication volume gradually increased, and the *H*-index remained consistently high, signaling the field's maturation and transition towards more systematic research. The second phase (2018–present) is marked by rapid development, with a sharp increase in annual publication volumes. Notably, 2020 saw a 25-article rise over 2019. This surge is largely attributed to the growing research output from leading countries, such as the USA and China, underscoring the increasing academic interest in TBS. This trend suggests that TBS research is poised to continue its robust growth in the foreseeable future.

This study spans 57 countries/regions. The USA maintains a significant lead in the field, with 180 publications, a total link strength of 147, and a Bc of 0.6, highlighting its core influence in TBS research. Despite ranking fifth in publication volume, the UK leads in citation count, indicating that its publications have garnered high academic quality and recognition despite lower output. China ranks second in publication volume but shows weaker performance in citation count, total link strength, and Bc, suggesting that TBS research in China is still in the early stages of development. Analysis of the co-occurrence network of countries/regions reveals the top five countries by Bc are

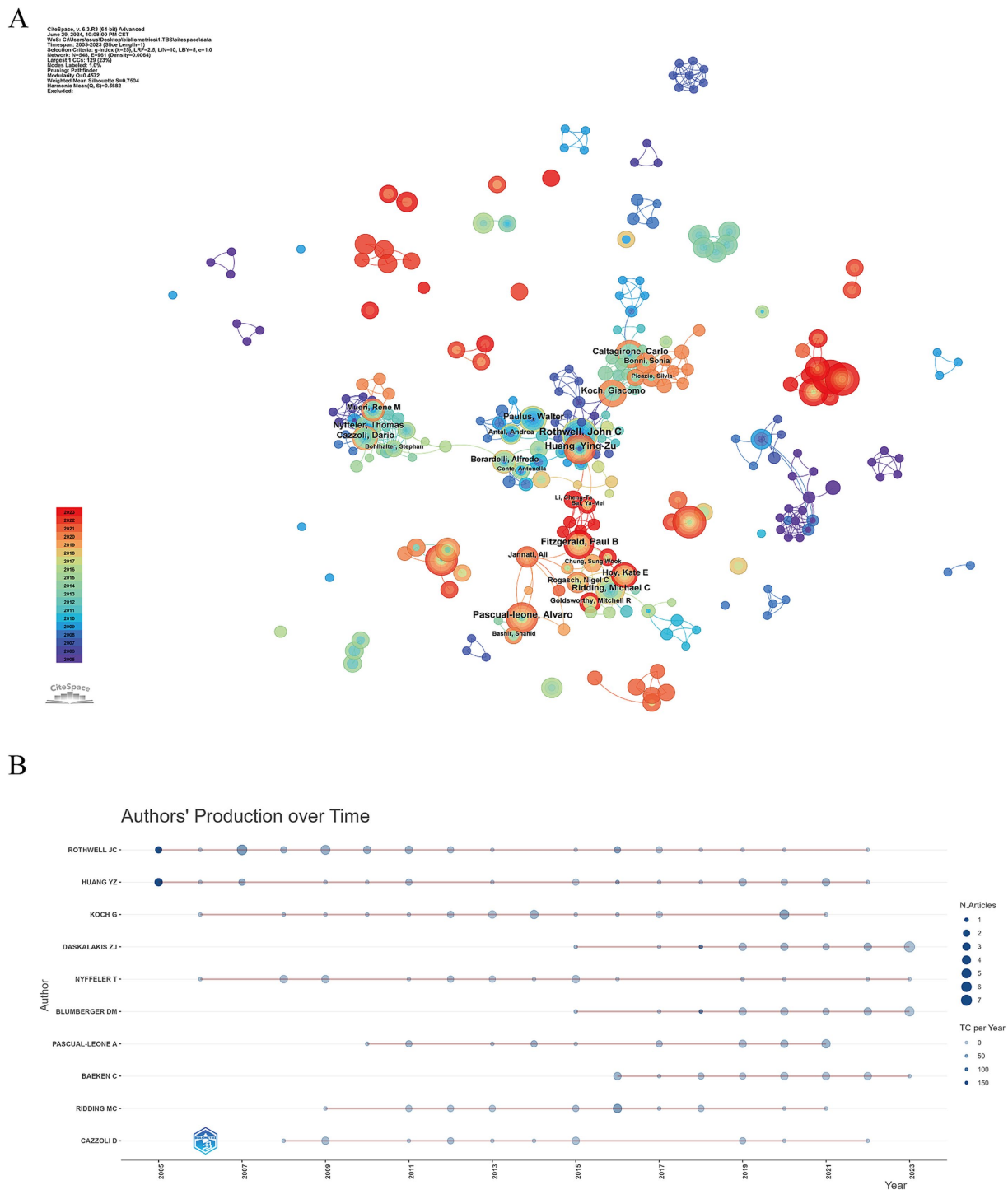

FIGURE 5
The author analysis of TBS-related research. **(A)** Co-occurrence authorship map of TBS research. **(B)** Annual publication trend of prolific authors.

the USA, the UK, Germany, Australia, and Canada, underscoring their pivotal roles in the TBS research collaboration network.

Among institutions, all of the top 10 have published over 20 articles. University College London leads in publication output and ranks first in Bc. Although not leading in publication volume, the University of California and Harvard University rank second and third, respectively, in Bc. This highlights their central roles in academic networking and fostering collaborations with other institutions. The co-occurrence network of institutions reveals diverse collaborative patterns among research entities across countries. While a substantial international network of cooperation exists, the majority of collaborations remain concentrated within national boundaries, suggesting the need for enhanced international academic exchanges moving forward.

TABLE 4 The top 10 journals publishing TBS-related publications (WoS).

Rank	Source	Country	Np	Nc	ACI	Impact factor (2023)
1	Brain Stimulation	USA	54	2,493	46.17	7.6
2	Clinical Neurophysiology	Netherlands	44	2,420	55.00	3.7
3	Frontiers in Neuroscience	Switzerland	34	397	11.68	3.2
4	Frontiers in Human Neuroscience	Switzerland	30	303	10.10	2.4
5	PLoS One	USA	28	594	21.21	2.9
6	Frontiers in Psychiatry	Switzerland	23	98	4.26	3.2
7	European Journal of Neuroscience	UK	21	827	39.38	2.7
8	Neuroscience Letters	Netherlands	20	454	22.70	2.5
9	NeuroImage	USA	17	517	30.41	4.7
10	Journal of Affective Disorders	Netherlands	15	318	21.20	4.9

Core authors have had a profound impact on TBS research, with their work frequently cited and playing a pivotal role in advancing the field. For instance, John C. Rothwell has emerged as a leading figure due to his extensive publications and critical contributions to research on motor cortex responses, which have influenced subsequent studies (23, 24). The co-occurrence map of core authors highlights distinct research teams within the TBS field, each led by prominent figures and comprising active scholars. However, collaboration between these teams remains limited, suggesting that further inter-team cooperation is essential for fostering broader development and innovation within the field. In this context, widespread collaboration between research institutions becomes particularly crucial. Such institutional partnerships can help alleviate the increasing costs associated with research infrastructure while promoting cooperation across specialized fields such as basic and clinical medicine. Additionally, these collaborations can serve as bridges, facilitating interactions among researchers and laying the foundation for new joint projects in diverse areas of research. By encouraging collaboration, institutional partnerships and joint projects can enable scientists and scholars to explore various research systems, institutions, and funding opportunities, thereby enhancing overall research capacity.

Analysis of journal data reveals that *Brain Stimulation* publishes the most TBS papers, followed by *Clinical Neurophysiology*, *Frontiers in Neuroscience*, and *Frontiers in Human Neuroscience*, which are also highly co-cited. These journals predominantly focus on neurophysiological mechanisms and diseases, which aligns with the findings from dual-map overlay analyses. This overlay method intuitively reveals journal geographic distribution, citation trajectory evolution, and shifts in research focus (25). The interdisciplinary citation patterns in TBS research demonstrate that journals in this field extend beyond their specific scopes, fostering academic exchange and knowledge integration across disciplines. Such integration plays a vital role in constructing knowledge systems and advancing scientific development. Utilizing *Bradford's Law* to categorize journals by publication count identifies core journals in TBS-related fields, enhancing research efficiency and supporting the construction of a cohesive knowledge system (15).

4.2 Hotspots and trends

Bibliometrics plays a pivotal role in processing and analyzing extensive datasets, providing researchers with valuable insights into emerging research trends (26). By examining shifts in frequently cited references and keywords, bibliometrics highlights key themes and facilitates a deeper understanding of the evolution within specific academic fields (27). Before delving into a detailed analysis, it is beneficial to first review the progression of TBS research from 2004 to 2023. Initially, research primarily focused on the paradigms of TBS, including preliminary investigations into its neurophysiological and pathological mechanisms. Over time, the focus expanded to include the molecular mechanisms and clinical applications of TBS in the treatment of various diseases, leading to a significant increase in related keyword and reference clusters. TBS research in disease treatment applications has largely concentrated on two key areas: (1) neurological rehabilitation: TBS has shown promise in enhancing motor and cognitive functions in post-stroke patients (28, 29), as well as in improving rehabilitation outcomes for individuals with aphasia (30), Parkinson's disease (PD) (31), spinal cord injury (32), and swallowing disorders (33). (2) Mental disorders: TBS has demonstrated potential efficacy in treating mental disorders, including depression (34, 35), schizophrenia (36), post-traumatic stress disorder (PTSD) (37), and obsessive-compulsive disorder (OCD) (38). The sustained scholarly focus on the physiological and pathological mechanisms of TBS in the context of various diseases has significantly advanced our understanding of its underlying molecular and cellular processes, while simultaneously underscoring its considerable clinical potential.

4.2.1 Mechanisms of TBS in neurophysiology and pathology

The ongoing scholarly focus on the physiological and pathological mechanisms of TBS in various diseases has considerably advanced our understanding of its underlying molecular and cellular processes, while also underscoring its significant potential for clinical application. Early research, as reflected in reference clustering #3 calcium-binding proteins and keywords clustering #6 synaptic plasticity, primarily focused on the physiological mechanisms of TBS, providing valuable insights into its biological basis. As research evolved, these clusters

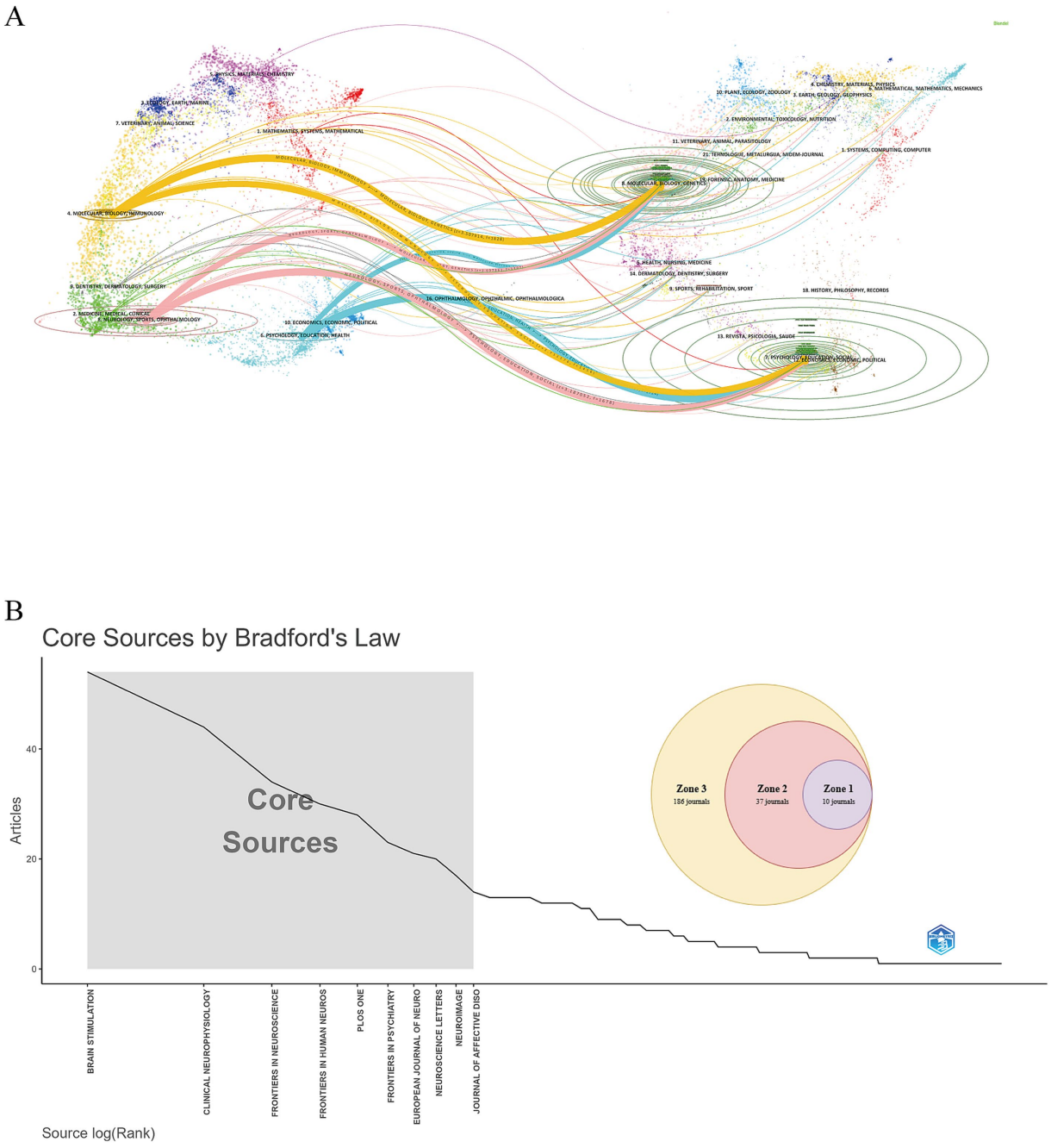

FIGURE 6
The journal analysis of TBS-related research. **(A)** Double-map overlay of TBS research journals. The left side depicts citing journal clusters, while the right side depicts cited journals, with colored trajectories indicating citation relationships. **(B)** Grouping of academic journals based on Bradford's Law.

gradually expanded to include disease-specific areas, such as #0 depression, #2 rehabilitation, #4 cerebellum, and #13 dysphagia. In terms of cognitive function, Wu et al. (39) found that cTBS enhances glymphatic fluid transport, particularly the exchange between cerebrospinal fluid and interstitial fluid. This process reduces amyloid-β deposition and enhances spatial memory cognition. Additionally, Sridharan et al. (40) demonstrated that TBS-induced $[Ca^{2+}]_i$ oscillations may activate gene expression related to memory. Another study suggests that iTBS can mitigate cognitive decline in an Alzheimer's disease mouse model by upregulating iron-sulfur cluster assembly, thus promoting mitochondrial respiration and function (41). In the context of Parkinson's disease (PD, keywords clustering #9), iTBS has been shown to reduce dopaminergic neuron degeneration, increase dopamine levels in the substantia nigra, and produce lasting effects on motor function (42). Research on stroke rehabilitation (reference clustering #2, keywords clustering #10) reveals that iTBS confers neuroprotection in ischemic stroke by reducing infarct volume and potentially suppressing neuronal apoptosis through miR-34c-5p regulation of the p53/Bax signaling pathway (43). Wu et al. (44) further demonstrated that cTBS treatment

TABLE 5 The top 10 most-cited references on TBS (WoS).

Rank	Title	First author	Year	Journal	Nc
1	Theta burst stimulation of the human motor cortex	Huang Y. Z.	2005	Neuron	2,758
2	Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial	Blumberger D. M.	2018	Lancet	609
3	The after-effect of human theta burst stimulation is NMDA receptor dependent	Huang Y. Z.	2007	Clinical Neurophysiology	431
4	Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects	Suppa A.	2016	Brain Stimulation	341
5	Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex	Di Lazzaro V.	2005	Journal of Physiology	285
6	Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity	Gentner R.	2008	Cerebral Cortex	282
7	Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex	Verbruggen F.	2010	Proceedings of the National Academy of Sciences of the United States of America	259
8	Theta-burst transcranial magnetic stimulation to the prefrontal cortex impairs metacognitive visual awareness	Rounis E.	2010	Cognitive Neuroscience	258
9	The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex	Di Lazzaro V.	2008	Journal of Physiology	241
10	Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation	Gamboa O. L.	2010	Experimental Brain Research	225

reduces the number of Iba-1-positive microglia and GFAP-positive astrocytes, modulating microglial polarization to reduce infarct volume. Additionally, iTBS may protect against motor deficits and neuronal damage caused by stroke by inhibiting the TLR4/NF-κB/NLRP3 signaling pathway, thereby regulating the M1/M2 phenotype balance in microglia (45). Studies focusing on magnetic resonance imaging in spinal cord injury (reference clustering #7) suggest that iTBS significantly increases serotoninergic nerve fibers at the injury site and promotes the growth of descending propriospinal fibers below the injury site. This suggests early neuroprotective potential and regenerative effects related to descending motor pathways (46). Furthermore, research on TBS gene polymorphisms has indicated that individual factors, such as gender, significantly influence the efferent properties of iTBS on neurogenesis. For example, iTBS increases the size of mossy fiber terminals forming synapses on CA3 pyramidal neurons in male mice (47). Additionally, individuals with the Val66Met genotype show more pronounced post-effects changes following cTBS compared to those with the Val66Val genotype (48). In conclusion, the physiological and pathological studies on TBS have revealed its multifaceted roles in regulating neural plasticity, improving cognitive function, promoting neural regeneration, and treating neurodegenerative diseases. These studies, through various molecular and cellular mechanisms, offer new strategies and insights for understanding and treating neuro-related diseases.

4.2.2 TBS in neurorehabilitation

Research in reference cluster #2 rehabilitation and keyword cluster #10 ischemic stroke has demonstrated the potential of TBS in enhancing motor function, cognitive function, and unilateral spatial neglect in post-stroke patients. Meng et al. (49) found that a combined treatment regimen of 1 Hz rTMS and iTBS enhances motor function in subacute stroke patients more effectively than 1 Hz rTMS alone. Additionally, ipsilesional cTBS has been shown to improve rehabilitation outcomes in patients with chronic post-stroke sequelae (50). In a comparison of iTBS and rTMS for motor function rehabilitation post-stroke, Huang (51) reported that while both methods were effective, iTBS significantly boosted rehabilitation efficiency. Systematic reviews and meta-analyses further support iTBS's potential to enhance motor and daily functions in stroke patients (4, 52–54). In terms of addressing cognitive impairment, Tsai et al. (55) demonstrated that iTBS improves global cognition, attention, and memory functions in patients with post-stroke cognitive impairment. For speech motor control in post-stroke patients, Szaflarski et al. (56) highlighted the therapeutic potential of iTBS in aphasia by stimulating the ipsilesional hemisphere. This view is supported by Zheng et al. (30), who found that cTBS modulates brain activity and connectivity, leading to enhanced language abilities in post-stroke patients. Meta-analytic findings also suggest positive effects of cTBS and iTBS on unilateral spatial neglect in post-stroke patients (57). The evolution of research in reference cluster #2 indicates a gradual expansion toward #13 dysphagia and #9 TMS-EEG, suggesting a future research focus on post-stroke dysphagia rehabilitation and the use of multimodal approaches, such as EEG and functional near-infrared spectroscopy, to validate TBS mechanisms.

Beyond stroke, TBS applications have also gained attention in spinal cord injury, aphasia, and PD rehabilitation. Fassett et al. (58) demonstrated that iTBS induces short-term neuroplastic changes in corticospinal output in spinal cord injury patients, while Feng et al. (32) showed that combining iTBS with physical therapy enhances

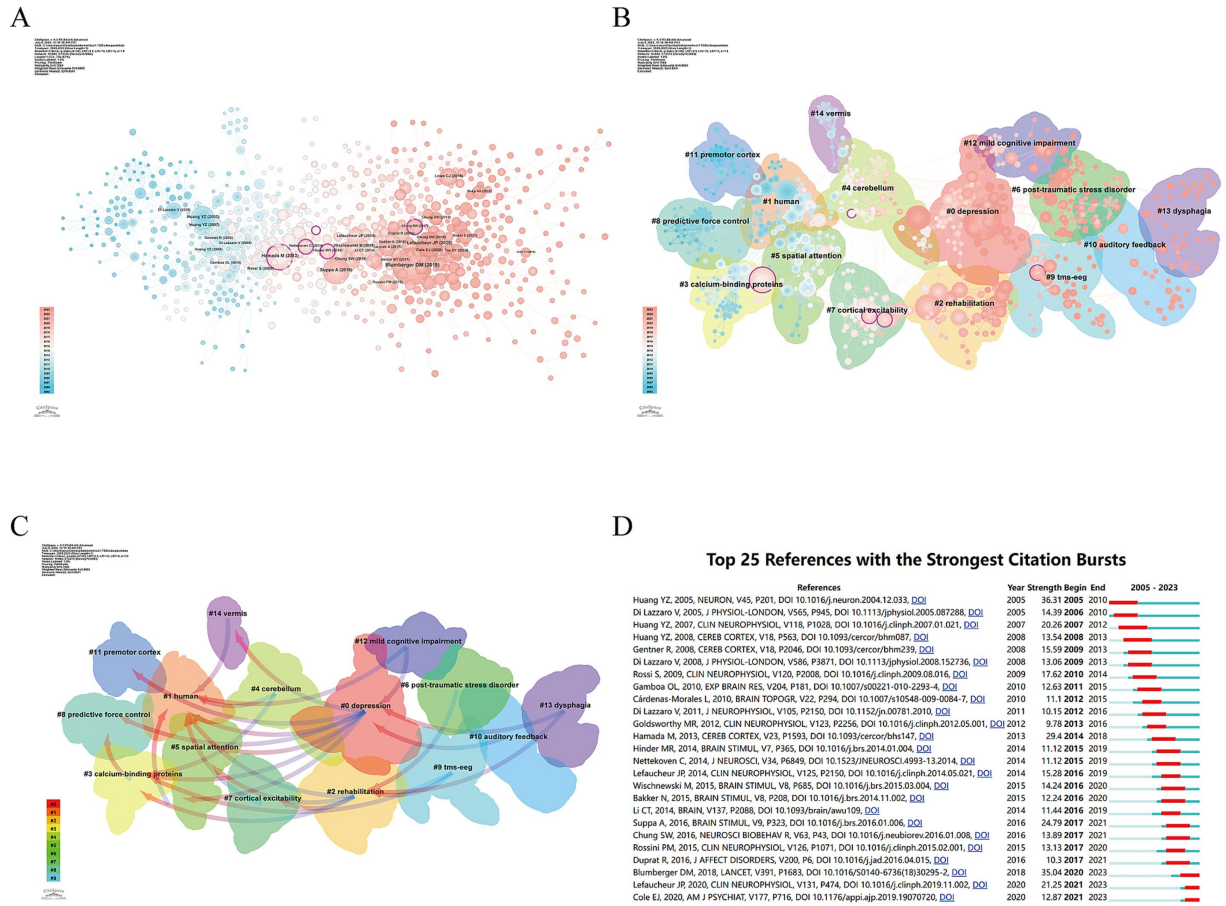

FIGURE 7
The reference analysis of TBS-related research. **(A)** Co-citation relationship map among references. **(B)** Clustering of references based on similarity, including 15 main clusters such as #0 depression, #1 human, #2 rehabilitation, etc. **(C)** Dependency analysis between literature clusters, reflecting the evolution process among them. **(D)** Top 25 references with the highest citation bursts, indicated by red lines in corresponding years.

lower limb motor recovery. Gharooni et al. (59) confirmed the safety and feasibility of iTBS for upper limb sensorimotor dysfunction in post-spinal cord injury patients. In aphasia treatment, Szaflarski et al. (60) observed combined therapy efficacy, and Zheng et al. (30) highlighted the potential of cTBS to enhance language abilities. In PD, Rashid-Lopez et al. (61) validated the benefits of iTBS on motor symptoms, while Degardin et al. (62) reported iTBS's effectiveness in reducing motor slowness. Additionally, continuous cTBS has been shown to alleviate levodopa-induced dyskinesia (63). Overall, TBS shows considerable therapeutic promise across these conditions, warranting ongoing exploration, though current research interest has not yet reached the level of stroke treatment.

4.2.3 TBS in the treatment of psychiatric disorders

TBS reference clustering #0 identifies depression as the largest cluster. The cluster evolution diagram reveals a progression from various research groups, eventually transitioning into cutting-edge studies, underscoring its pivotal role in current research trends. Depression, a prevalent and severe mental health disorder, has long been a central focus of mental health treatment. Research suggests that TBS offers promising potential for alleviating depressive symptoms. Both cTBS and iTBS have demonstrated beneficial effects on mood, cognitive functions, and specific symptoms in patients with depression (64–67). Within the depression-related keyword cluster, research on the design of TBS targets and their combination with other treatments remains a primary area of exploration. For example, some studies propose that iTBS, when combined with D-cycloserine, may enhance clinical response and remission rates in patients with major depressive disorder (68). Another study suggests that, despite the limited sample size and number of studies, both cTBS and iTBS show preliminary efficacy in treating treatment-resistant depression and depressive episodes in bipolar disorder (69). Furthermore, bilateral burst TMS has been shown to significantly reduce depressive symptoms and may also improve brain responses associated with emotion processing (70). These findings provide compelling scientific evidence supporting the effectiveness and safety of TBS as a treatment for depression and offer guidance for future clinical applications and large-scale studies on TBS in depression treatment.

Examining the references and keyword clusters concerning the application of TBS in psychiatric disorders beyond depression, research has primarily focused on schizophrenia, PTSD, and OCD. In schizophrenia, Tyagi et al. (71) demonstrated that cTBS might alleviate auditory hallucinations by modulating cortical excitability, while iTBS shows promise in reducing negative symptoms, particularly when applied to the cerebellar vermis. For PTSD, iTBS has been shown to

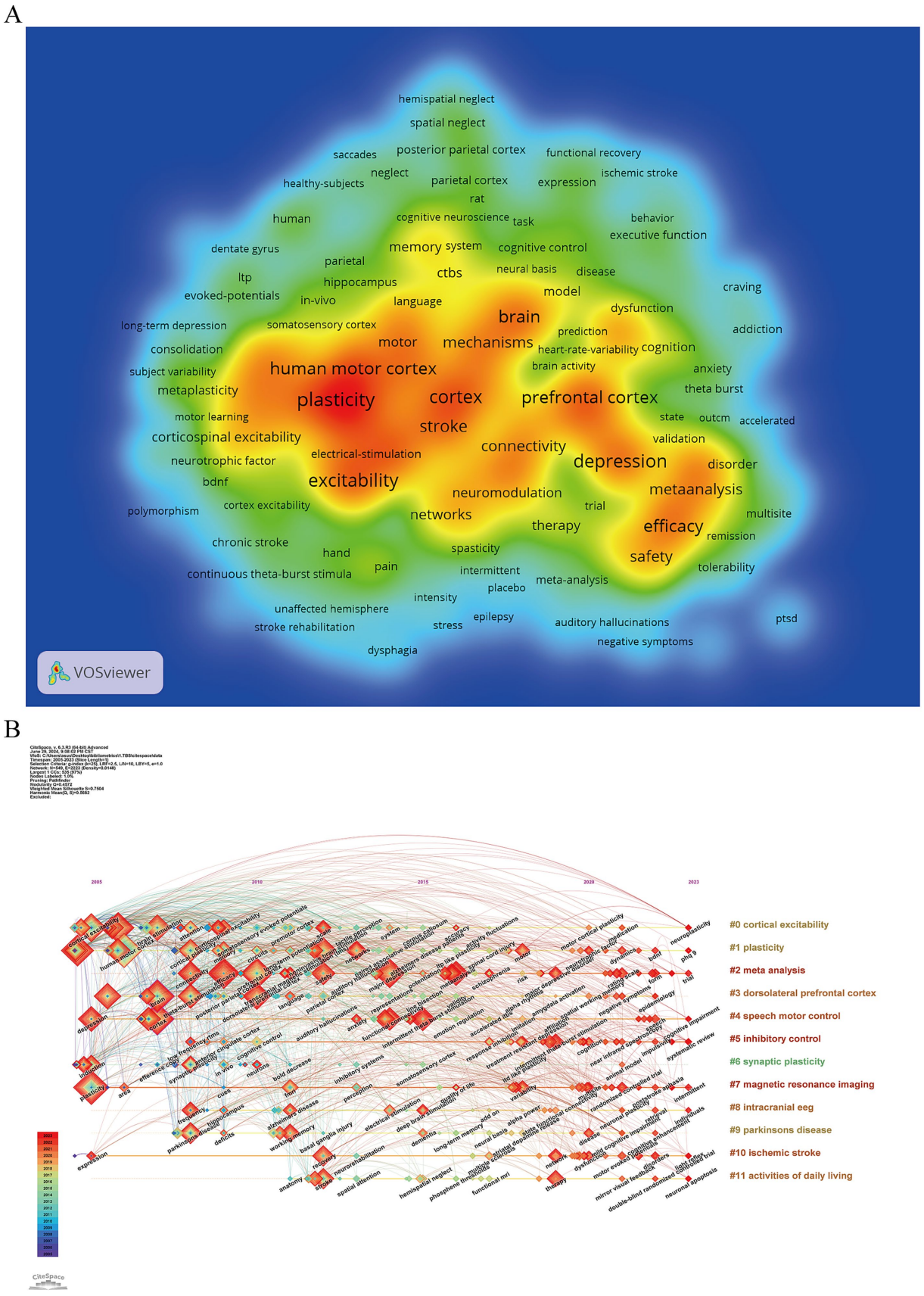

FIGURE 8
The keyword analysis of TBS-related research. **(A)** Co-occurrence network of keywords in TBS research. **(B)** Timeline view of keyword clusters.

be as effective as traditional 10 Hz rTMS, and as a short-term treatment, it significantly improves core PTSD symptoms (72). Additionally, a case study suggests that TBS targeting the bilateral dorsolateral prefrontal cortex may offer significant improvements in severe PTSD symptoms, particularly when these symptoms co-occur with depression (73). These findings introduce new strategies for the clinical treatment of PTSD and emphasize the necessity for further research to explore the long-term effects and optimal application protocols of TBS in PTSD treatment. In OCD, cTBS targeting the bilateral supplementary motor area has been shown to markedly improve clinical symptoms (74). Moreover, cTBS stimulation of the orbitofrontal cortex demonstrates good safety and tolerability, with significant improvements in anxiety symptoms and overall severity (75). As the clinical application of TBS expands, research in these areas is likely to become a prominent future trend.

4.2.4 The therapeutic potential of cerebellar TBS

Reference clusters #4 cerebellum and #14 vermis provide an overview of studies investigating the cerebellum as a potential target for TBS. The cerebellum, a crucial constituent of the central nervous system, plays an indispensable role not only in the regulation of motor control but also in the mediation of cognitive and emotional processes (33). Halko et al. (76) demonstrated that TBS applied to specific cerebellar areas, including the lateral crus I/II and vermal lobule VII, modulates brain networks, such as the default mode network and the dorsal attention system, thereby underscoring the cerebellum's pivotal role in regulating large-scale neural circuits. Furthermore, cerebellar TBS has shown promising results in improving gait and balance in patients with multiple sclerosis (77), enhancing visuomotor learning in stroke survivors (29), alleviating negative symptoms in schizophrenia (36), boosting upper-limb sensory-motor function following spinal cord injury (59), and reducing dyskinesia in Parkinson's disease (63). Within the broader context of TBS research, these findings align with prior studies focusing on other brain regions, such as the motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC), while also expanding the scope of research in these domains. Early meta-analyses and systematic reviews have underscored the therapeutic efficacy of TBS in these regions for a variety of conditions, including motor rehabilitation, cognitive enhancement, and emotional regulation (4, 78, 79). For instance, TBS targeting M1 has been extensively investigated for its potential to improve motor function following stroke (80). Similarly, TBS applied to the DLPFC has shown promise in the treatment of depression, with evidence suggesting that it modulates DLPFC activity to improve both emotional and cognitive functions (81). These studies indicate that, despite targeting different brain regions, TBS exerts its therapeutic effects by modulating specific neural networks and pathways. However, the cerebellum, often overshadowed by the motor cortex and prefrontal cortex in TBS research, offers distinct advantages due to its dual role in both motor and non-motor processes. Thus, the exploration of cerebellar TBS not only complements existing studies on M1 and DLPFC, but also opens novel avenues for therapeutic innovation, underscoring the urgent need for further investigation into the cerebellum's role in brain network modulation and its potential for treatment.

4.3 Limitations

This study has several limitations. First, all data were sourced exclusively from the WoSCC. While the WoSCC covers a broad spectrum of scholarly publications, it is possible that some relevant studies were omitted from the analysis. Second, the variability in the quality of the articles included in the dataset may affect the reliability of the results. Furthermore, the study predominantly focused on English-language papers and reviews, which introduces the potential for language bias and quality discrepancies, potentially undermining the robustness of the analysis. Lastly, the bibliometric analysis software used in this study has inherent limitations. Specifically, the extraction and clustering of terms from titles, abstracts, and keywords may introduce variability, and there is no guarantee that terms with similar meanings will be grouped consistently.

5 Conclusion

In conclusion, global research on TBS continues to progress rapidly, with the USA emerging as a significant contributor to the field. Among influential journals, Brain Stimulation has established itself as a key publication in this domain. Prominent researchers such as Huang Y. Z. and John C. Rothwell have made substantial contributions to TBS studies. Current research is particularly focused on the clinical applications of TBS in neurorehabilitation and depression, as well as investigations into the underlying mechanisms. These areas are expected to remain central to future research efforts. Future trends may increasingly explore TBS applications for conditions such as dysphagia, cognitive impairments, and PTSD. Notably, TBS cerebellar stimulation has emerged as a promising therapeutic approach for addressing psychiatric and cognitive issues. This bibliometric analysis provides an objective overview of the TBS field, offering valuable insights to scholars tracking the evolution of the knowledge base and research directions in this area.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

MiL: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. SJ: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. MeL: Formal analysis, Methodology, Resources, Writing – original draft, Writing – review & editing. BY: Formal analysis, Investigation, Writing – review & editing. QW: Formal analysis, Writing – review & editing. CF: Investigation, Writing – review & editing. ZL: Supervision, Validation, Writing – review & editing. LW: Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1469877/full#supplementary-material

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Trends in exercise therapy research for neurological diseases: a bibliometric and visualization approach from 2000 to 2024

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Background: Neurological disorders are one of the major global health burdens, and exercise therapy has been widely recognized as a beneficial intervention. However, the existing literature has primarily focused on summarizing the interventions, complications, and influencing factors, with relatively limited systematic comparisons and summaries.

Methods: This study employed a bibliometric analysis approach, using VOSviewer and CiteSpace software to analyze the literature on the application of exercise therapy in neurological disorders from 2000 to 2024, including annual publication volumes, countries/regions, institutions, authors, journals, keyword co-occurrences, keyword clustering, keyword timelines, and keyword bursts.

Results: The study found that the United States is the leading contributor in this field, and the University of Toronto and the University of Illinois are the most active research institutions. Keyword analysis revealed that the research hotspots in this field are concentrated on the role of exercise therapy in the prevention, treatment, rehabilitation, and improvement of quality of life for neurological disorders, and are gradually delving into its potential physiological mechanisms.

Conclusion: This study provides valuable references for subsequent research in this field, helping to track the research frontiers and predict future research directions. Future research could further explore the specific mechanisms and clinical efficacy for different neurological diseases, providing more targeted evidence for clinical practice.

KEYWORDS

exercise therapy, neurological diseases, bibliometrics, visualization, CiteSpace, VOSviewer

1 Introduction

The central nervous system (CNS), consisting of the brain and spinal cord, plays a crucial role in integrating the received information and coordinating various bodily functions (1). These neurological conditions encompass a wide range, including neurodevelopmental disorders, age-related neurodegenerative diseases, and emerging illnesses such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, and post-COVID-19 cognitive impairment. According to a report published in The Lancet, an estimated 3.4 billion (95% UI 3.20–3.62) individuals worldwide were affected by neurological disorders in 2021, accounting for 43.1%

(40.5–45.9) of the global population (2). Central nervous system diseases impose a significant health burden, resulting in mortality and disability (3). In 2021, neurological disorders were the leading cause of global disease burden, surpassing even cardiovascular diseases, and accounted for 443 million disability-adjusted life years (DALYs) lost due to disease, disability, and premature death (2). Additionally, factors such as stress, unhealthy lifestyles, work-rest imbalances, and environmental pollution can contribute to the development of neurological disorders across all age groups (4).

Physical activity (PA) has been widely recognized as a valuable intervention for various neurological conditions. Exercise therapy, a subcategory of PA, is a planned, structured, and repetitive activity with the ultimate or intermediate goal of improving or maintaining physical health (5). The 2018 review published in JAMA found that PA can promote healthy growth and development, enhance mood, cognitive function, and sleep quality, as well as lower the risk of various chronic diseases (6). A 2019 review found that exercise interventions have shown therapeutic benefits for a range of neurological disorders, including Parkinson's disease, Huntington's disease, and Alzheimer's disease, regardless of the specific type and intensity of exercise (7). Furthermore, a 2021 meta-analysis revealed that exercise therapy has been shown to effectively improve aerobic capacity and muscle strength in the management of multiple sclerosis (8). Moreover, a 2020 review further underscored the diverse potential benefits of exercise for Alzheimer's disease, including the prevention of associated risk factors (e.g., vascular dysfunction, obesity, diabetes) as well as the promotion of brain health, particularly through the muscle-brain axis (5). In recent years, there has been an increasing volume of research on the use of exercise therapy for the management of neurological disorders. However, the existing literature has mainly focused on summarizing the interventions, complications, and influencing factors, with relatively limited systematic comparisons and overviews of the current status and trends in this research area. Although this field has seen numerous review articles, traditional narrative reviews often rely on subjective assessments, lacking a quantitative approach. Such research methods that are based on personal experiences or biases can result in a less accurate and comprehensive evaluation of the current situation and trends (9).

Bibliometric analysis has become a widely adopted approach to identify research hotspots, analyze research outputs, and reveal trends. This is achieved by visualizing the internal connections among various pieces of information in the form of knowledge maps (10). Tools such as VOSviewer and CiteSpace have become essential for bibliometric studies. VOSviewer, co-developed by Professors Waltman and van Eck at Leiden University in the Netherlands, offers powerful visualization capabilities (11). On the other hand, CiteSpace is a web-based Java application created by Professor Chen's team at Drexel University in the United States. It is specifically designed for data analysis and visualization, featuring a unique keyword burst detection function (12).

This study utilized VOSviewer and CiteSpace software to perform a bibliometric analysis of the literature on the application of exercise therapy in neurological disorders, covering the period from 2000 to 2024. The analysis examined various aspects, including annual publication volumes, countries/regions, institutions, authors, journals, keyword co-occurrences, keyword clustering, keyword timelines, and keyword bursts. This comprehensive analysis aimed to investigate the current status and research focal points in this field from both spatial and temporal perspectives. The findings are expected to help track the research frontiers and predict future research directions, thereby providing a valuable reference for subsequent studies in this domain.

2 Materials and methods

2.1 Searching strategy

The data analyzed in this study were extracted from the Web of Science Core Collection (WoSCC), a database published by Clarivate Analytics. To cover as many relevant articles as possible, we selected terms that are commonly used in the scientific literature to construct the search strategy. Terms linked to exercise therapy and neurological disorders were obtained from the Medical Subject Headings (MeSH) in the PubMed database for the purposes of this research. On May 19, 2024, a literature search was conducted, and the complete search strategy is presented in the Supplementary Table S1. The final dataset comprised 1,234 records, which were exported as plain text files, including information on publication year, title, author names, institutions, abstracts, keywords, and journal names.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) the intervention population must be diagnosed with a neurological disorder; (2) research specifically addressed exercise therapy; (3) clinical studies on humans and should be published in English in the form of articles; (4) the article type was limited to original articles or reviews; (5) studies were published between January 1, 2000, and May 19, 2024.

Exclusion criteria: (1) the articles that did not pertain to exercise therapy in neurological disorders were excluded; (2) non-article formats, such as letters, were excluded; (3) articles written in languages other than English were excluded.

2.3 Data collection

The data curation and screening process for this study involved the following steps: (1) two reviewers from the team independently assessed the articles, removing those that did not align with the research focus. Any discrepancies were resolved through discussion. (2) The affiliations and country names were corrected and standardized to minimize the impact on the results. (3) The keywords were also standardized, as non-standardized keywords with variations in word forms, plurals, and singular versions could lead to the appearance of meaningless repetitions in the keyword co-occurrence analysis. For example, "Turkey" and "Türkiye" were unified as "Turkey," "England" and "Scotland" were unified as "UK," and "meta-analysis," "metaanalysis," and "Metaanalysis" were all standardized as "meta-analysis."

2.4 Data analysis

The bibliometric data extracted from the database was stored in "download_*.txt" files for subsequent analysis. We employed Microsoft

Excel to examine temporal trends in publication output. For the construction of visual network maps, we utilized VOSviewer version 1.6.18. This software, which implements a probabilistic data standardization method, enabled us to create comprehensive visualizations of publishing countries, contributing organizations, prominent authors, key journals and highly cited references. In these visualizations, node size correlates with connection degree, frequency of occurrence, and connection strength. The thickness of connecting lines represents the intensity of collaboration between nodes. Node colors denote distinct clusters within the network. This approach allowed for a multifaceted analysis of the research landscape in our field of study.

To construct knowledge mapping visualizations, we employed CiteSpaceV 6.3.R1 software. The analysis parameters were configured with time slicing set to 1, covering a temporal range from 2000 to 2024 at annual intervals. We utilized a time-based similarity algorithm to generate two key visualizations: timeline plots and keyword burst analysis. Timeline plots, presented as clustering diagrams, illustrate the historical evolution patterns of keyword-associated clusters, providing a chronological perspective on the field's development. Keyword burst analysis serves as a crucial indicator for identifying emerging research trends, highlighting sudden increases in the usage frequency of specific terms. The integration of these two analytical approaches facilitated a comprehensive examination of shifts in research focal points over time and potential future trajectories within the field. This dual-method strategy allowed for a nuanced understanding of both the historical context and the emerging dynamics in our research domain.

3 Results

3.1 Analysis of annual publications

As shown in Figure 1A, the publication output in the field of neurological disorders treated with physical therapy has been on an upward trend from 2000 to 2024. The annual publication volume can be roughly divided into three stages. During the period from 2000 to 2009, the annual publication count remained below 25 papers. From 2010 to 2016, the average annual publications increased to 42,

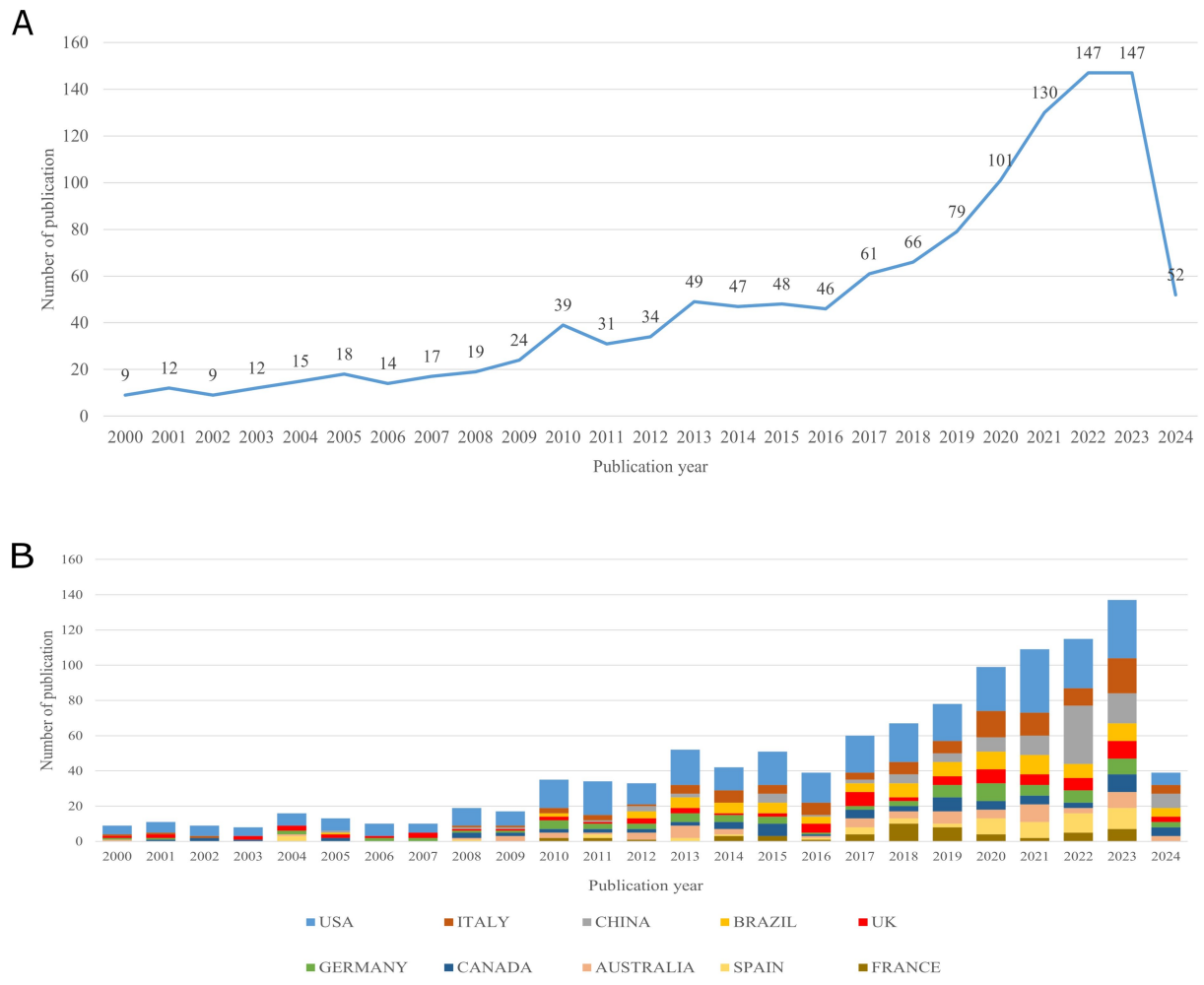

FIGURE 1
(A) Trends in the number of publications on exercise therapy in neurological disorders. **(B)** The growth trends of the top 10 productive countries on exercise therapy in neurological disorders.

indicating growing attention in this research area. After 2016, the publication output increased dramatically, suggesting a significant rise in the research focus on this topic.

3.2 Analysis of countries/regions

Based on the analysis using VOSviewer, a total of 66 countries/regions have published articles in this research field. Only the United States has published more than 150 papers. There are 39 countries/regions that have published more than 5 papers. Table 1 summarizes the publication output and betweenness centrality of the top 10 most productive countries/regions. The United States ranks first in terms of publication volume (376), followed by Italy (116), China (104), Brazil (94), and the United Kingdom (87). Betweenness centrality is used to describe the influence of a country in this field, and a value greater than 0.1 indicates significant impact. According to the betweenness centrality, the United States (0.31), Germany (0.19), and the United Kingdom (0.15) are considered to have a significant influence in this field, even though the publication volume of the UK and Germany are not among the highest. The top 5 countries/regions in terms of total citations are the United States (17,730), Canada (3,913), Italy (3,240), the United Kingdom (3,154), and Germany (2,953). The top 5 countries in terms of total link strength are the United States, the United Kingdom, Italy, Canada, and Germany.

Figure 1B depicts the stacked bar chart showing the publication output growth trend of the top 10 most productive countries in this field from 2000 to 2024. The chart shows that the United States has the highest publication output, with a sustained upward trend. Italy and China are the next two most prolific, having begun focusing on this field around 2008. However, China's growth has been particularly rapid, now approaching the levels of the United States and Italy. Figure 2A illustrates the collaborative landscape among nations and regions that have made substantial contributions to this research domain, specifically those with more than five publications. The visualization reveals eight distinct clusters among these 39 countries and regions, with interconnecting lines denoting co-authorship relationships. The varying thickness of these connections represents the intensity of collaboration, quantified by the total link strength (TLS) between each pair of countries or regions.

3.3 Analysis of institutions

Institutional collaboration network analysis using the VOSviewer software, we analyzed the institutional collaboration in the research field of applying movement therapy to neurological disorders. The analysis identified a total of 2,233 institutions involved in this research area. Figure 2B illustrates 72 of these institutions that have published at least 5 papers and collaborated with other institutions formed 11 distinct clusters. Table 2 presents the top 10 most prolific institutions in this research field. The list is led by the University of Toronto, followed by the University of Illinois, University of Washington, University of São Paulo, University of British Columbia, University of Milan, University of Sydney, University of Melbourne, Harvard Medical School, and the University of Alabama at Birmingham. This ranking reflects a global distribution of research excellence, spanning North America, South America, Europe, and Oceania.

Institutional research productivity and collaboration patterns according to the data presented in Table 2, the University of Toronto was the most prolific institution, contributing 18 publications, followed by the University of Illinois (17 publications) and the University of Washington (15 publications) in the United States. Overall, the top-ranking institutions were primarily from the United States, Australia, and Canada, indicating their leading roles in this research field. The analysis of institutional collaborations revealed that the University of Toronto, Columbia University, and the University of Washington had the strongest link strengths, suggesting a greater emphasis on inter-institutional collaborative research (Figure 2B).

3.4 Analysis of authors and co-cited authors

Our VOSviewer-based author analysis yielded significant insights into the field's key contributors. Table 3 presents a comprehensive overview of the 15 most productive researchers and the 17 most cited scholars (with ties at the 17th position). The majority of high-output authors hail from the United States, Brazil, and various European nations, while the most cited researchers are

TABLE 1 Top 10 countries/regions in number of papers published in exercise therapy in neurological disorders.

	Countries/regions	Documents	Centrality	Total citation	Total link strength
1	USA	376	0.21	17,979	198
2	Italy	116	0.12	3,294	105
3	People's Republic of China	104	0.06	1,266	32
4	Brazil	94	0.06	1,170	37
5	UK	87	0.25	3,197	117
6	Germany	82	0.22	2,995	87
7	Canada	75	0.04	3,954	90
8	Australia	71	0.1	2,665	70
9	Spain	60	0.08	1,277	74
10	France	52	0.04	1,968	76

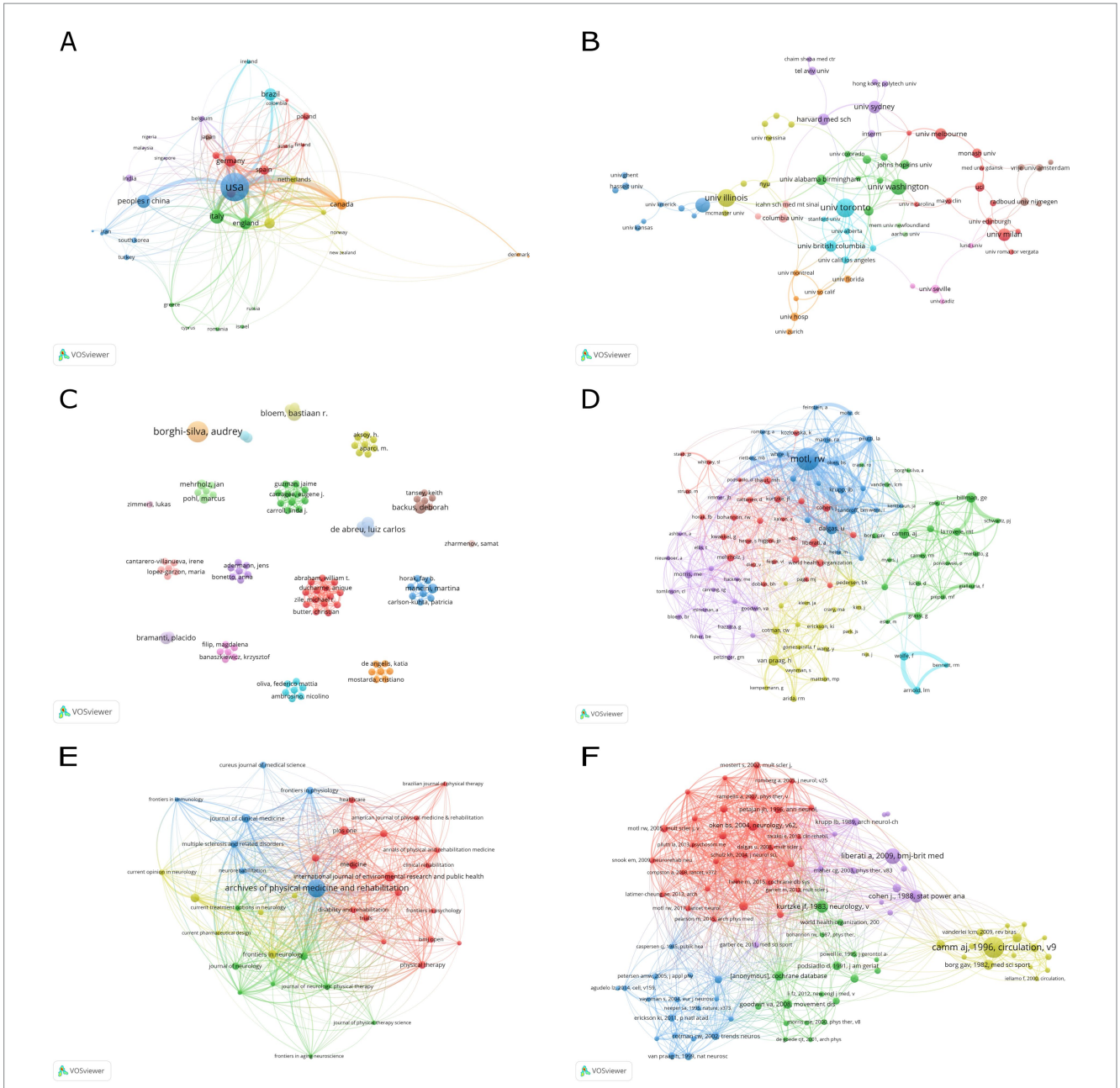

FIGURE 2
(A) Countries/regions cooperation analysis. **(B)** Institutions cooperation analysis. **(C)** Authors cooperation analysis. **(D)** Co-cited author analysis. **(E)** Journal analysis. **(F)** Co-references analysis. The node size indicates the number of publications; the color of the nodes indicates the clusters; the lines between the nodes indicate the existence of a collaborative relationship, and the thicker the line indicates the closer the relationship.

predominantly based in the United States. Figure 2C depicts the collaborative networks among researchers with a minimum of three publications. Although large-scale collaborations were not evident, several smaller research clusters emerged. Notably, Motl, Robert W. stands out as the field's leading contributor, boasting 10 publications and 616 citations, securing his position at the apex of both productivity and impact metrics. Figure 2D illustrates the interconnections among 107 researchers who have garnered over 20 citations each. Motl, Robert W. stands out with a clear lead over other highly cited authors, indicating his substantial contributions and influential role in this field.

3.5 Analysis of journals

Our journal analysis, conducted using VOSviewer, identified 39 journals that have contributed significantly to this research field, each publishing a minimum of 5 articles. Table 4 highlights the top 10 most influential journals in this domain. Leading the list is *Archives of Physical Medicine and Rehabilitation*, which has made the most substantial contribution with 38 publications, accumulating an impressive 2,476 citations. Following closely is the *International Journal of Environmental Research and Public Health*, with 16 articles and 121 citations. These journals hold prominent positions in the field,

TABLE 2 Top 10 institutions in number of papers published in exercise therapy in neurological disorders.

	Institution	Documents	Total citations	Total link strength	Country
1	University of Toronto	18	1,479	17	Canada
2	University of Illinois	17	833	8	America
3	University of Washington	15	1,399	10	America
4	University of São Paulo	14	218	5	Brazil
5	University of British Columbia	12	527	13	England
6	University of Milan	12	432	8	Italy
7	University of Sydney	12	364	9	Australia
8	University of Melbourne	11	514	5	Australia
9	Harvard Medical School	11	248	7	America
10	University of Alabama at Birmingham	10	230	10	America

TABLE 3 Top 15 authors in number of papers published and top 17 co-citied authors in exercise therapy in neurological disorders.

	Author	Documents	Total citations	Country		Co-cited author	Co-cited	Total link strength	Country
1	Motl, Robert W.	10	616	America	1	Motl, Robert W.	191	2,022	America
2	Borghi-Silva, A.	8	125	Brazil	2	Dalgas, Ulrik	77	1,001	Denmark
3	Bloem, Bastiaan R.	5	258	Netherlands	3	Van Praag, Henriette	65	345	America
4	De Abreu, Luiz C.	5	58	Brazil	4	Camm, Alan J.	64	250	England
5	Calabro, Rocco S.	5	34	Italy	5	Billman, George E.	62	408	America
6	Schlaich, Markus P.	4	265	Australia	6	Wolfe, Frederick	52	296	America
7	Dalgas, Ulrik	4	208	Denmark	7	Liberati, Alessandro	49	189	Italy
8	Langeskov-Christensen, M.	4	208	Danmark	8	Morris, Meg E.	47	364	Australia
9	Backus, Deborah	4	134	America	9	Krupp, Lauren B.	45	345	America
10	Feys, Peter	4	97	Belgium	10	La Rovere, Maria T.	45	320	Italy
11	Kool, Jan	4	67	Switzerland	11	Cohen, Jacob T.	44	227	Israel
12	Watts, Christopher R.	4	48	America	12	Arnold, Lesley M.	43	233	America
13	Raimundo, Rodrigo D.	4	42	Brazil	13	Thaut, Michael H.	43	141	Canada
14	Ploughman, Michelle	4	28	Canada	14	Cotman, Carl W.	41	310	America
15	Bramanti, Placido	4	12	Italy	15	Grassi, Guido	41	186	America
					16	Mehrholz, Jan	41	162	Germany
					17	Pedersen, Bente K.	41	395	Denmark

TABLE 4 Top 10 journals in number of papers published in exercise therapy in neurological disorders.

	Source	Documents	Total citations	Total link strength	IF (2023)
1	Archives of Physical Medicine and Rehabilitation	38	2,494	1,220	3.6/Q1
2	International Journal of Environmental Research and Public Health	16	123	344	4.6/Q2
3	Medicine	15	40	220	1.3/Q2
4	International Journal of Molecular Sciences	13	253	218	4.9/Q1
5	PLoS One	13	106	197	2.9/Q1
6	Journal of Clinical Medicine	13	105	277	3/Q1
7	Frontiers in Neurology	12	163	423	2.7/Q2
8	Cureus Journal of Medical Science	12	16	47	1/Q3
9	Cochrane Database of Systematic Reviews	11	1,018	599	8.8/Q1
10	Physical Therapy	11	368	246	3.5/Q1

IF, impact factor.

being widely cited. The publication landscape of these 39 journals is visually represented in Figure 2E, revealing four distinct clusters. The journal landscape in this field exhibits a degree of clustering, with a few core journals being heavily cited, alongside more specialized, independent journals.

3.6 Analysis of highly cited and bursting references

The bibliometric analysis revealed a total of 72,843 references, with 95 of them being cited more than 10 times. Table 5 presents the detailed information of the top 10 most cited references. The reference with the highest number of citations is "Heart rate variability—standards of measurement, physiological interpretation, and clinical use," which has been cited 63 times. This is followed by "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement" (43 citations) and "Statistical power analysis for the behavioral sciences" (33 citations). Figure 2F depicts the co-citation network of the 95 highly cited references. Furthermore, a reference burst analysis was conducted using CiteSpace, with the threshold parameter *Y* set to 0.5 and other parameters maintained at default values. This analysis identified 20 references exhibiting significant citation bursts, which are presented in Figure 3A. The visualization indicates that the highly cited articles are predominantly published within the past decade, suggesting an emerging influx of high-quality publications in this field in recent years.

3.7 Analysis of keyword co-occurrence

The keyword co-occurrence analysis was conducted using CiteSpace, with the time slicing set to 1 and the top N keywords selected as 5. The resulting network included a total of 426 nodes and 1,332 links. Due to the density of the initial network, a pruning process was performed. Additionally, to address the issue of different author representations of the same keywords, node merging was carried out to consolidate synonymous terms. The resulting keyword co-occurrence network is presented in Figure 3B, where the purple outer ring indicates a betweenness centrality value greater than or equal to 0.1 for the corresponding node. Table 6 presents a comprehensive analysis of the 20 most significant keywords, ranked according to three key metrics: frequency of occurrence, betweenness centrality, and chronological order of initial appearance in the literature. The keywords with a betweenness centrality greater than or equal to 0.1 include "exercise" (0.36), "physical activity" (0.11), "rehabilitation" (0.1), "therapy" (0.13), "autonomic nervous system" (0.25), and "heart rate variability" (0.11). The main research types for exercise therapy in the neurological disorders are randomized controlled trials and double-blind studies. The primary disease areas investigated include multiple sclerosis, Parkinson's disease, stroke, and spinal cord injury. The key research themes revolve around exercise, quality of life, physical activity, rehabilitation, therapy, autonomic nervous system, balance, heart rate variability, physical therapy, health, and gait.

3.8 Analysis of keyword clustering

We employed CiteSpace software to perform keyword clustering analysis. The log-likelihood ratio (LLR) algorithm was utilized to categorize keywords into distinct thematic groups. The resulting network comprised 25 clusters, of which the top 10 clusters were selected for further analysis (Figure 3C). The modularity (*Q*) of 0.8124 and the weighted mean silhouette (*S*) of 0.9009 indicate that the keyword clustering modules derived from the data are statistically significant and highly reliable. The timeline analysis of the keyword clustering (Figure 3D) and the summary of the key terms associated with the top 10 clusters (Table 7) provide insights into the research themes and trends. Focusing on Cluster #0, which is related to

TABLE 5 Top 10 co-references in number of papers published in exercise therapy in neurological disorders.

	Title	Year	Citations	Source/IF (2022)	First author	Type	Reference
1	Heart rate variability—standards of measurement, physiological interpretation, and clinical use	1996	63	Circulation/35.5/Q1	Camm, Alan J.	Guideline	(46)
2	Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement	2009	43	Annals of Internal Medicine/19.6/Q1 European Heart Journal/37.6/Q1	Moher, David	Guideline	(47)
3	Statistical power analysis for the behavioral sciences	1988	33		Cohen, Jacob	Book	(48)
4	Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS)	1983	32	Neurology/7.7/Q1	Kurtzke, John F.	Article	(49)
5	Randomized controlled trial of yoga and exercise in multiple sclerosis	2004	26	Neurology/7.7/Q1	Oken, B. S.	Article	(50)
6	Psychophysical bases of perceived exertion	1982	25	Medicine & Science in Sports & Exercise/4.1/Q1	Borg, Gunnar A. V.	Symposium	(51)
7	The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis	2008	23	Movement Disorders/7.4/Q1	Goodwin, Victoria A.	Review	(52)
8	Heart-rate recovery immediately after exercise as a predictor of mortality	1999	22	New England Journal Of Medicine/96.2/Q1	Cole, Christopher R.	Article	(53)
9	Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development	2013	21	Archives of Physical Medicine and Rehabilitation/3.6/Q1	Latimer-Cheung, Amy E.	Review	(54)
10	The timed "Up & Go": a test of basic functional mobility for frail elderly persons	1991	21	Journal of the American Geriatrics Society/4.3/Q1	Podsiadlo, Danie	Article	(55)

IF, impact factor.

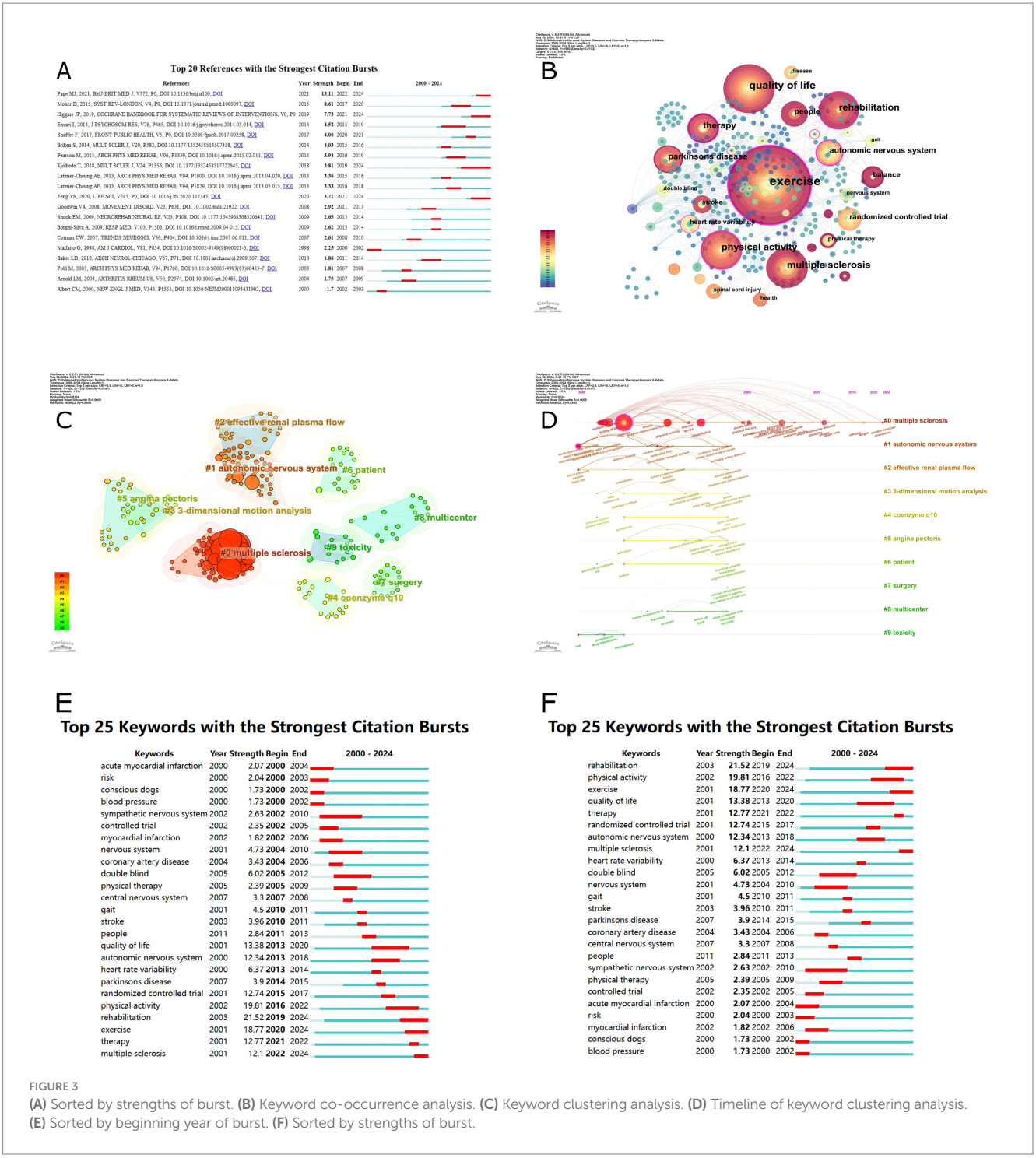

FIGURE 3
(A) Sorted by strengths of burst. **(B)** Keyword co-occurrence analysis. **(C)** Keyword clustering analysis. **(D)** Timeline of keyword clustering analysis. **(E)** Sorted by beginning year of burst. **(F)** Sorted by strengths of burst.

"multiple sclerosis," the silhouette value of 0.527 suggests a well-defined and reliable cluster. The main topics covered by Cluster #0 include multiple sclerosis, physical activity, myocardial infarction, autonomic nervous system, and quality of life.

3.9 Analysis of keyword burst

A keyword burst analysis was conducted using CiteSpace, with the threshold parameter Y set to 0.5 and other parameters maintained at default values. This analysis identified 25 keywords exhibiting significant bursts. Figure 3E presents the data sorted by the beginning year of the research burst, while Figure 3F shows the data sorted by the strength of the research burst. From 2000 to 2011, keywords such as "double blind," "nervous system," "gait," "stroke," and "coronary artery disease" were commonly cited, with burst strengths reaching 6.02, 4.73, 4.5, 3.96, and 3.43, respectively. However, from 2012 to 2024, the focus shifted to "rehabilitation," "physical activity," "exercise," "quality of life," and "therapy," with burst strengths reaching 21.52, 19.81, 18.77, 13.38, and 12.77,

TABLE 6 Keywords in top 20 research on exercise therapy for neurological disorders.

	Keywords	Frequency	Centrality	Year		Keywords	Frequency	Centrality	Year
1	exercise	379	0.36	2001	11	balance	27	0	2005
2	quality of life	155	0.09	2001	12	heart rate variability	21	0.11	2000
3	multiple sclerosis	102	0.04	2001	13	stroke	20	0.06	2003
4	physical activity	99	0.11	2002	14	physical therapy	14	0.01	2005
5	rehabilitation	87	0.1	2003	15	disease	12	0.02	2003
6	therapy	66	0.13	2001	16	spinal cord injury	12	0.09	2003
7	Parkinson disease	47	0.02	2007	17	double blind	11	0.05	2005
8	autonomic nervous system	39	0.25	2000	18	health	11	0.07	2003
9	people	37	0	2011	19	nervous system	11	0.02	2001
10	randomized controlled trial	33	0.06	2001	20	gait	8	0.06	2001

TABLE 7 Top 10 keyword clusters.

Clusters	Size	Silhouette	Keywords
#0	54	0.527	multiple sclerosis; physical activity; myocardial infarction; autonomic nervous system; quality of life
#1	45	0.825	autonomic nervous system; myocardial infarction; heart rate variability; coronary artery disease; multiple sclerosis
#2	25	0.976	effective renal plasma flow; atrial natriuretic peptide; verapamil; norepinephrine; glomerular filtration rate
#3	23	0.994	3-dimensional motion analysis; joint position sense; nursing home residents; controlled clinical trial; functional reach
#4	19	0.98	coenzyme q10; encephalopathy; melas mitochondrial myopathy; strokelike episodes; mitochondrial encephalomyopathies
#5	19	0.942	angina pectoris; nitrates; cluster headache; glyceryl trinitrate; nitric oxide
#6	18	0.999	patient; incompetence; knowledge; acquisition; insufficiency
#7	17	1	surgery; platelet aggregation inhibitors; anesthetics; drug withdrawal; plants
#8	17	1	multicenter; blind crossover trial; education; placebo; amitriptyline
#9	15	0.902	toxicity; drug interactions; pentoxifyiline; peripheral diseases; pharmacokinetics

respectively (Figure 3E). Keywords associated with rehabilitation medicine and high-quality research methods have experienced a concentrated burst of citations in the past decade, indicating growing attention from leading experts and scholars in the rehabilitation field (Figure 3F).

4 Discussion

To our knowledge, this study presents the first comprehensive bibliometric analysis of research trends in exercise therapy for neurological disorders. A total of 1,224 publications from the WoSCC database, spanning the period from January 1, 2000 to May 19, 2024, were analyzed. The analyses, conducted using VOSviewer 1.6.18 and CiteSpace 6.3.R1, examined the temporal and spatial distribution, institutional and author contributions, and top journals in the field. Additionally, keyword analysis, cluster analysis, and burst hotspot analysis were used to identify current research hotspots and frontiers.

4.1 General description

The temporal analysis revealed a steady increase in publications over the years, with around 15 times more articles published in 2023 compared to 2000. The number of published studies remained consistently over 100 during the 2020–2023 period, suggesting a promising trend in this field, potentially driven by the high prevalence of neurological disorders. The relatively low publication output from 2000 to 2009 indicates that the study of exercise therapy for neurological conditions was in its early stages, followed by a gradual increase from 2010 to 2016, and a significant rise after 2017.

The United States was the leading contributor in this field, accounting for 33.76% of the total publications, which may be attributed to the early start of research in this area in the country (Table 1). The centrality values for the United States, Germany, and the United Kingdom were above 0.1, underscoring a significant emphasis on academic cooperation by researchers in these regions.

The United States led in the number of publications and total citations, emerging as the most collaborative country in the study of neurological disorders. This was attributed to a higher intensity of research compared to other nations. The Netherlands followed, ranking second in both the number of publications and levels of cooperation. Western countries and regions have exhibited strong cooperation, whereas the relatively low total link strength observed in China and Brazil indicates the need for further enhancement in research efforts. Furthermore, nearly all of the top 10 institutions are from countries or regions with the highest number of publications (Table 2), highlighting the robust academic capabilities of these nations in this field. Among the top 10 most prolific institutions, four were American.

Motl, Robert W., a professor at the University of Illinois Chicago, is the most prolific author in this field from the United States (Table 3). With an *H*-index of 75, he has made a substantial impact on the research community. Motl, Robert W. has been cited a total of 191 times and has a link strength of 2022, far exceeding other authors (Figure 2D). An analysis of Motl's, Robert W. published papers reveals his focus on the diagnosis, treatment, rehabilitation, and quality of life for individuals with multiple sclerosis. He emphasizes that exercise can be an effective rehabilitation strategy to manage symptoms, restore function, enhance quality of life, promote overall wellness, and increase participation in daily activities (13). The most frequently cited article in this field is by Motl et al. (14). This study validated the Patient Determined Disease Steps (PDDS) as a reliable patient-reported outcome (PRO) measure of disability in multiple sclerosis (MS). The findings of this study have significantly influenced both clinical practice and subsequent research in the field.

The impact factor serves as a key metric for assessing journal quality. Among the top 10 most productive journals in this field, the Cochrane Database of Systematic Reviews stands out with the highest impact factor of 8.4. Its 11 published articles have garnered 1,018 citations, demonstrating the high quality and peer recognition of its publications (Table 4). Our analysis of the published literature reveals that this journal primarily focuses on high-quality systematic reviews, serving as a pivotal database for healthcare-related meta-analyses. It's worth noting that journals across the impact factor spectrum play crucial roles in advancing exercise therapy for neurological disorders.

According to Table 5 and Figures 2F, 3A show that most of the highly cited articles were published 10 years ago, while most of the articles with high citation bursts were published in the last 10 years, indicating that this field is gradually attracting the attention of research scholars, and it may be a popular trend for future research.

4.2 Hot spots and frontiers

Keywords serve as the author's distillation and generalization of the article's content, reflecting its core focus. Analyzing keyword bursts can identify changes in research hotspots and emerging trends within a field. Multiple sclerosis (MS) has been a subject of intense focus and ongoing research among experts in the field (Figure 3D). Since 2015, the research hotspots have primarily focused on randomized controlled trials (15–18), physical therapy (19–22), rehabilitation (23, 24), exercise (7, 21), treatment (25, 26), and multiple sclerosis (27–29) (Figure 3E). These research areas have been widely studied and applied in both academia and clinical practice in recent years. Understanding these research hotspots can help develop targeted research plans and provide valuable references for academic exploration in the relevant fields.

An analysis of keywords over the past quarter-century reveals key research trends in exercise therapy for neurological conditions. One prominent focus has been the etiology of these disorders. For instance multiple sclerosis (MS) has been identified as an autoimmune condition characterized by central nervous system demyelination (30, 31). Regular exercise can exert anti-inflammatory effects in chronic inflammatory diseases such as MS by reducing pro-inflammatory cytokines and promoting anti-inflammatory cytokines thereby helping to modulate MS progression (32, 33). Parkinson disease (PD) is characterized by death of dopaminergic neurons in the substantia nigra. These include early onset of rapid eye movement sleep behavioral deficits and decreased sense of smell as well as late progression to the substantia nigra and other midbrain and basal forebrain structures (34). Parkinsonian symptom progression is directly proportional to autonomic dysfunction and postganglionic sympathetic damage is its main cause (35). According to a recent review type I muscle fibers are distinctly affected in MS and PD. In MS the impact is primarily on metabolic functions while in PD the effects are more pronounced in the structural characteristics of these fibers (36). (1) The evidence-based foundation and potential mechanisms of exercise therapy in neurological disorders. For patients with mild to moderate MS exercise therapy can increase aerobic capacity and muscle strength and improve the ability to perform activities of daily living while reducing fatigue and depressive states (37, 38). Exercise therapy has been shown to be beneficial in improving cognitive function and walking mobility among individuals with MS (39, 40). Aquatic therapy is considered an emerging therapeutic modality that can improve the quality of life in patients with MS (41). The long-term effects of exercise interventions on biological parameters (Irisin, BDNF, IL-6) are relatively modest in patients with MS (42). In Parkinson's patients different forms of exercise therapy are beneficial for different movement aspects including gait and balance training aerobic exercise progressive resistance exercise treadmill exercise strength training tai chi and integrated exercise (7, 34). Research indicates that exercise therapy can mitigate damage to dopaminergic neurons in the midbrain and enhance basal ganglia function. This is achieved through adaptive changes in dopamine and glutamate neurotransmission. Consequently patients with early to mid-stage Parkinson's disease may experience improved overall functionality and walking efficiency (37). High-intensity exercise therapy may prevent vascular dementia and Alzheimer's disease but there is only modest evidence showing its significant impact on improving activities of daily living and cognition in people with dementia (37). Recent studies have shown that aerobic exercise improves cognitive and ADL and that combined exercise significantly improves strength fitness and balance functions in AD patients (7). This may be related to the fact that exercise therapy promotes an increase in the volume of the hippocampus as well as inducing anti-inflammatory effects (37).

(2) Research on the effects of exercise therapy on the complications of neurological disorders. Exercise therapy has been demonstrated to be effective in improving depressive states and fatigue syndrome in patients with MS (43, 44). Interventions including gait and balance training as well as home-based or leisure exercise are effective in reducing fear of falling in individuals with PD and MS, respectively (45).

5 Conclusion

This study employed bibliometric analysis to comprehensively examine the current status and development trends of exercise therapy research in the field of neurological disorders. The results show that research in this field has been growing continuously, with countries such as the United States, Italy, and China leading in terms of paper output and academic influence. Keyword analysis indicates that the research hotspots in this field are concentrated on the role of exercise therapy in the prevention, treatment, rehabilitation, and improvement of quality of life for neurological disorders, and are gradually delving into its potential physiological mechanisms. This study provides valuable references for subsequent research in this field. In the future, this field may further focus on the application of exercise therapy in the personalized management and multidisciplinary collaboration of neurological disorders, providing more evidence for clinical practice.

6 Limitations

This study has the following limitations: (i) the study focused solely on the research trends of exercise therapy in the field of neurological disorders, without delving deeper into the specific mechanisms and clinical efficacy for different neurological diseases. Future research should further explore the underlying physiological mechanisms of exercise therapy to provide more targeted treatment strategies. (ii) This study only analyzed the published literature in the Web of Science database, which may have omitted relevant studies published in other databases or in non-English languages. A more comprehensive search strategy across multiple databases could provide a more complete picture of the research landscape. (iii) This study mainly adopted quantitative bibliometric analysis methods, lacking in-depth discussion of the research content and quality. Future research could combine qualitative research methods, such as systematic reviews and expert interviews, to present a more comprehensive understanding of the current status and development trends in this field, and provide more valuable references for clinical practice.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

JZ: Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. LZ: Conceptualization, Formal analysis, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1479731/full#supplementary-material

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Electrotherapy as treatment for chemotherapy-induced peripheral neuropathy — a randomized controlled trial

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Background: Electrotherapy has been investigated in chronic pain and diabetic peripheral neuropathy, however prospective trials in patients with chemotherapy-induced peripheral neuropathy (CIPN) are scarce.

Methods: Fifty-one patients with CIPN ≥ grade 1 subsequent to receiving platinum- and/or taxane-based chemotherapy types were randomized to 8 weeks of high tone external muscle stimulation (HTEMS) or transcutaneous electrical nerve stimulation (TENS). The primary outcome were changes in the EORTC-QLQ-CIPN20 questionnaire. Secondary outcomes included clinical examinations, a classification of CIPN according to CTCAE v 4 and the EORTC-QLQ-C30 questionnaire. A control group (n = 17) receiving no intervention was recruited retrospectively.

Results: The EORTC-QLQ-CIPN20 sensory and motor scales improved in both intervention groups (TENS: −12.3pts and − 8.2pts; HTEMS: −14.7pts and − 8.2pts) with no significant changes in the control group −3.3pts; −2.8pts. The changes in the sensory scale differed significantly between the HTEMS and the control group. In the EORTC-QLQ-C30 questionnaire, there was a significant improvement for physical functioning in the HTEMS group only (+7.9pts) with no between group differences. CIPN classification according to CTCAE v4 improved significantly in both intervention groups.

Conclusion: Home-based electrotherapy with HTEMS or TENS were successful in improving CIPN-related sensory impairment and could therefore provide a powerful treatment for this side-effect of chemotherapy.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT03978585

KEYWORDS

HTEMS, TENS, high tone therapy, QLQ-CIPN20, QLQ-C30

1 Introduction

Continuous advancements in diagnosis and treatment of cancer lead to rising numbers of cancer survivors and to increasing life expectancy (1). However, the progress in systemic therapy also brings challenges in the management of side effects. Chemotherapy-induced peripheral neuropathy (CIPN) is one major complication of several anti-cancer therapies, especially of taxanes and platinum salts (2). Additionally, the problems may increase with novel drug types like antibody-drug conjugates and checkpoint inhibitors (3, 4). In a meta-analysis of studies investigating taxanes and platinum salts, the average prevalence of CIPN was >60% in the first 3 months after cessation of chemotherapy and about 30% after 6 months and beyond (5). The severity of CIPN depends on the chemotherapeutic agent, the cumulative dose, and the treatment regime. Symptoms usually begin during chemotherapy at a lower intensity and tend to increase if chemotherapy is continued. As a result, dose reductions and ultimately discontinuation of chemotherapy are frequently necessary in order to avoid high-grade CIPN, that hampers daily activities and diminishes quality of life (6). Unfortunately, there is still no effective pharmacological or non-pharmacological treatment of CIPN available. Several approaches with antidepressants, antiepileptics, magnesium, calcium, vitamins E and B6, glutamine, glutatione, N-acetyl-ysteine, omega-3 fatty acids, alpha lipoic acid, topical ketamine, acupuncture, or magnetic field therapy failed to show reproducible and significant relief of symptoms (7–9).

Electrotherapy is a potential approach for alleviating symptoms in this population. Transcutaneous electrical nerve stimulation (TENS) has shown analgesic effects in various chronic pain conditions by increasing opioid receptor activation and restoring central inhibition (10–13). A single-arm, uncontrolled trial including 29 patients with CIPN showed that 6 weeks of TENS reduced sensory and motor impairments as well as pain (14). However, high level evidence is missing (15). Similarly, treatment with high-tone external muscle stimulation (HTEMS) seems a promising approach in the therapy of CIPN. Compared to TENS, HTEMS works with higher frequencies and might therefore also enhance blood circulation and cellular metabolism rather than only suppressing pain perception (16). This method is successfully used in the treatment of diabetic neuropathy (17, 18) and shows better results in the reduction of pain compared to TENS (16). To the best of our knowledge, there is one very recent (2024) placebo-controlled trial using HTEMS as treatment for CIPN indicating its potential by improving paresthesia and mental stress after 3 weeks of electrotherapy with no changes for the placebo group. However, this study was underpowered ($n = 7$ per group) and changes in sensory or motor impairments assessed with the EORTC QLQ-CIPN20 questionnaire did not reach significance (19). Hence, the objective of this randomized controlled clinical trial was to investigate the effectiveness of home-based electrical therapy in the treatment of CIPN. We hypothesized that both interventions (HTEMS and TENS) would mitigate CIPN symptoms and increase quality of life, with superior results for HTEMS.

2 Materials and methods

2.1 Setting

This was a single-blinded, randomized controlled trial with an observation time of 8 weeks. The trial was conducted at the University Hospital Salzburg from September 2019 until March 2023. The study protocol was approved by the ethics committee of Salzburg County (ID 415-E/2376/7–2018). All processes were performed in accordance with the 1964 Helsinki declaration and all patients gave their written informed consent. The study was registered in Clinical Trials, available at https://clinicaltrials.gov/ct2/show/NCT03978585. The study protocol was previously published in detail (20). However, after publication of the protocol the following amendments have been made: (1) in addition to patients with breast and colorectal cancer, individuals with other types of cancer were allowed to participate; (2) patients with CIPN ≥ grade 1 at baseline were included and (3) a control group fulfilling the same inclusion and exclusion criteria, but receiving no intervention for CIPN was recruited retrospectively. The reporting of this clinical trial follows the CONSORT guidelines (see CONSORT checklist in Supplementary material S5).

2.2 Study-flow

For the original study, CIPN patients were recruited, randomized and treated either with HTEMS or TENS therapy from September 2019 until October 2021. The control group, where patients received no intervention, was recruited in retrospect from July 2022 to March 2023.

2.3 Patient identification and recruitment

All patients receiving systemic tumor treatment at the IIIrd Medical Department of the Paracelsus Medical University Salzburg underwent screening for neuropathy complaints by using a standardized admission form or by collecting medical history orally. For inclusion, patients had to have completed chemotherapy with a taxane or platinum salt for a confirmed invasive cancer 4 to 24 weeks before, have a clinical diagnosis of CIPN ≥ grade 1 according to Common Terminology Criteria for Adverse Events version 4 (CTCAE v 4), be at least 18 years of age and have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to1. The CTCAE v 4 questionnaire includes the limitations of the activities of daily living and has 5 categories: 0 = no impairment, 1 = loss of deep tendon reflexes and paresthesia, 2 = limiting instrumental activities of daily living, 3 = limiting self-care ADL, 4 = life-threatening consequences. Exclusion criteria contained an ongoing or planned treatment with antitumor treatments with potentially neurotoxic side effects, preexisting peripheral neuropathy, peripheral arterial occlusive disease > grade 1, skin conditions preventing proper application of electrodes or implanted medical electronic devices (e.g., pacemaker).

2.4 Randomization and blinding

Participants were randomly allocated to either HTEMS or TENS. Randomization was performed centrally. The random allocation sequence was generated using the random number generator available online.[1] Subjects were stratified according to the respective chemotherapeutic agent: taxane or platin. Physicians responsible for the clinical examinations and outcome assessment were blinded. Due to the technical design of the intervention, participants and device instructors could not be blinded. Patients in the control group were not randomized or blinded and did not receive any electrotherapy for CIPN symptoms. For this group, the statistician analyzing the data was blinded to the patient's allocation.

2.5 Intervention and control

Participants of the intervention groups received instructions on the proper use of the electrical device and the first treatment under supervision. The further applications were carried out at home. After 1 week of use, a therapist called the patients to ensure proper use. Patients of both groups were instructed to use the electrical device daily for at least 30 min for 8 weeks. The minimum requirement of use for the per protocol analysis was at least 5 days a week corresponding to a total usage time of ≥1,200 min. To ensure the minimum requirement, frequency and duration of use were recorded in a diary filled out by the patients and on the electrical device.

HTEMS was administered using a HiTOP 191 device (gbo Medizintechnik, Rimbach, Germany). The conductive rubber electrodes were placed on the lower limbs (one at the calf and one on the sole of the foot). If the hands were also affected, patients were additionally allowed to perform the electrical therapy on the hands with electrodes placed on the frontal side of the forearm and on the back of the hand. The principle of HTEMS is based on muscle contraction in intervals. An interval comprised 3 sec of ramp-up time (where intensity increases to the pre-set maximum level), followed by 3 sec of holding time (where intensity remains at maximum), and finally, 3 sec of pause (with no stimulation). The applied frequencies varied in the same predefined order from 4,096 to 32,768 Hertz over three octaves in 72 quarter-tone steps of 1 sec each for each patient. The maximum intensity of the stimulation was initially set by a medical technician to a level that elicited tolerable muscle contractions without causing any pain or discomfort and was continually adjusted by the patient in order to maintain this effect.

Patients in the TENS group placed the rubber electrodes of the electric device (DoloBravo, MTR GmbH, Berlin, Germany) on the same body areas as described for the HTEMS electrodes. The manufacturer's predefined applied frequency was 80 Hertz. The maximum intensity of the stimulation was set the same way as described for the HTEMS therapy.

A control group was recruited retrospectively to control for time-dependent symptom relief and to avoid overestimation of intervention effects. They completed the EORTC-QLQ-CIPN20 and EORTC-QLQ-C30 questionnaires twice, with an interval of 8 weeks and did not receive any electrotherapy within this period.

2.6 Outcomes

All outcome parameters were evaluated at baseline (T0) and at the end of the study, after 8 weeks of treatment (T1). The primary endpoint was the improvement in the disease specific EORTC-QLQ-CIPN20 questionnaire. This questionnaire contains 20 items assessing sensory (9 items), motor (8 items), and autonomic symptoms (3 items), using a 4-point Likert scale (1 = "not at all," 2 = "a little," 3 = "quite a bit," and 4 = "very much"). All scale scores are linearly converted to a 0 to 100 scale (0 = no sensory impairment, 100 = worst sensory impairment) (21). A difference of ≥5.9 points was considered clinically significant (22). Secondary endpoints were improvements of the patient quality of life (EORTC-QLQ-C30) and the classification of CIPN grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4 (23). Clinician-reported secondary outcomes were assessed in the HTEMS and the TENS group with a standardized clinical test battery containing the following assessments: Vibration sensibility measured with a semi-quantitative tuning fork (24), Achilles and patellar tendon reflexes (25), temperature sensibility (26), perception of touch, by symmetrically stroking the patient's thighs, lower legs and feet with the physician's fingers (27) and strength of the lower leg muscles (by performing toe standing/walking and heel standing/walking on both feet; possible, not possible). A detailed description of the clinical assessments can be found in the Supplementary Tables S4–S6.

Patients in the control group did only complete the EORTC-QLQ-CIPN20 and EORTC-QLQ-C30 questionnaires. No other outcome parameters were recorded.

2.7 Statistical analysis

Sample size was calculated *a priori* for a power of 80%, $\alpha = 0.05$ and $\beta = 0.20$, proposing a 5.9 point difference in pre-post changes of the EORTC-CIPN20 scores between both treatment groups. Using an estimated standard deviation of 5.5, a sample size of 42 patients (21 per arm) would be required. Considering an estimated drop-out rate of 15%, we defined a recruitment goal of 50 patients.

The analysis for the primary endpoint was based on the intention-to-treat principle, secondary endpoints were analyzed per protocol. Normal distribution of data was assessed by the Shapiro–Wilk test. Between-group differences at baseline were analyzed using a student's t-test for independent and normal distributed data and a Mann–Whitney U-Test or a Chi-square test for nonparametric data. Within-group differences were calculated using a student's t-test for paired samples if data was normally distributed, otherwise a Wilcoxon signed-rank test was used. *p*-values were Bonferroni corrected. Pre-post changes between groups were analyzed using a Kurskal Wallis test for the EORTC-QLQ-CIPN20 and EORTC-QLQ-C30 questionnaires (all data not normally distributed). If a significant effect was found, Mann–Whitney U-Tests were performed post-hoc with Bonferroni corrected *p*-values. Within-group differences for all other secondary endpoints were analyzed using a Wilcoxon signed-rank

1 https://www.sealedenvelope.com/simple-randomiser/v1/lists

test or a McNemar test, respectively. Pre-post differences between groups for the CTCAE v4 CIPN grade were analyzed using a Mann–Whitney U-Test test. All tests were 2-tailed, and a 5% probability level was considered as significant. All statistical analyses were performed with IBM SPSS Statistics 23.0 (IBM, Enhingen, Germany). Figures were created using GraphPad prism v.9 (GraphPad Software, Boston, United States).

3 Results

In total, 51 patients were included between September 2019 and October 2021 and randomized to the TENS or HTEMS group. One patient in the HTEMS group died during the study period due to his cancer and was not included in the intention-to-treat analyses for the primary outcome EORTC-QLQ-CIPN20 questionnaire ($n = 50$). Three patients in the HTEMS group and five patients in the TENS group were not included in the per-protocol analysis for secondary outcomes ($n = 42$), because they did not achieve the minimal total usage time for electrical therapy ($\geq$ 1,200 min). The retrospectively recruited control group (CON) consisted of 10 male and 7 female (in total $n = 17$) patients. The study flow and the baseline characteristics of patients are demonstrated in Figure 1 and Table 1.

There were no baseline differences between groups except for the distribution of type of neurotoxic chemotherapy ($p = 0.049$) with higher percentage of platinum in the control group (Table 1). Baseline EORTC-QLQ-CIPN20 values in the autonomic scale also differed significantly between the three groups: patients in the TENS group had lower baseline values than patients in the two other groups. Baseline values for sensory scale showed a large numerical difference between the control and both intervention groups (CON 36 vs. TENS 47 vs. HTEMS 45), however this was not statistically significant ($p = 0.213$) (Table 2; Figure 2).

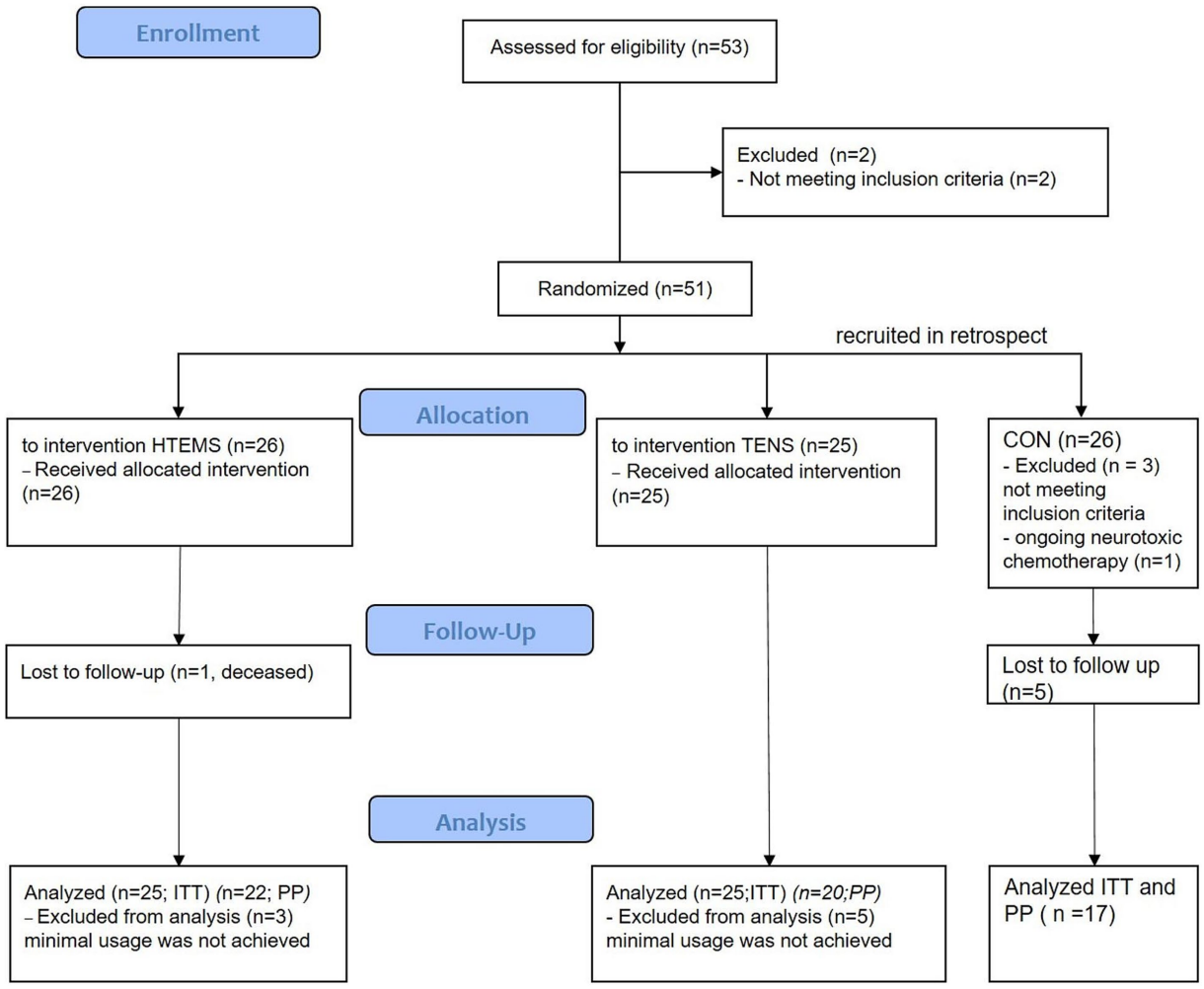

FIGURE 1
Flow diagram of the study. HTEMS: high tone external muscle stimulation; TENS: transcutaneous electrical nerve stimulation, both groups recruited and treated from September 2019 until October 2021; CON: control group, recruited in retrospect from July 2022 to March 2023; ITT: intention to treat analysis for primary outcome; PP: per protocol analysis for secondary outcomes.

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TABLE 1 Baseline tumor and patient characteristics.

	HTEMS *n* = 25	TENS *n* = 25	Controls *n* = 17	*p*- value
Median age [years] (range)	63 (36–89)	69 (24–81)	63 (47–79)	0.748
Age < 60y	6 (24%)	11 (44%)	4 (23%)	
Gender				0.832
Male	10 (40%)	12 (48%)	10 (59%)	
Female	15 (60%)	13 (52%)	7 (41%)	
Tumor entity				0.922
Breast cancer	11 (44%)	10 (40%)	5 (29%)	
Colorectal cancer	4 (16%)	6 (24%)	5 (29%)	
Esophageal cancer	2 (8%)	3 (12%)	2 (12%)	
Pancreatic cancer	1 (4%)	4 (16%)	2 (12%)	
Gastric cancer	2 (8%)	2 (8%)	2 (12%)	
Other	5 (20%)	0 (0%)	1 (6%)	
Tumor AJCC stage				
I	3 (12%)	3 (12%)	2 (12%)	0.543
II	6 (24%)	8 (32%)	4 (23%)	
III	8 (32%)	2 (8%)	5 (29%)	
IV	8 (32%)	12 (48%)	6 (35%)	
Grade				0.910
1–2	12 (48%)	11 (44%)	6 (35%)	
3	7 (28%)	10 (40%)	6 (35%)	
Unknown	6 (24%)	4 (16%)	5 (30)	
Therapeutic setting				
Curative	16 (64%)	15 (60%)	11 (65%)	0.939
Palliative	9 (36%)	10 (40%)	6 (35%)	
Neurotoxic chemotherapy*				0.049
Taxane	12 (48%)	11 (44%)	6 (35%)	
Platinum#	8 (32%)	9 (36%)	8 (47%)#	
Taxane and Platinum	5 (20%)	5 (20%)	3 (18%)	
Mean duration of neurotoxic chemotherapy [days] (SD)	104 (34)	134 (101)	143 (72)	0.193
Median duration [days] (range)	105 (140)	89 (477)	170 (270)	
Early discontinuation because of CIPN	10 (40%)	8 (32%)	3 (18%)	0.308
Mean time after ending of neurotoxic chemotherapy [days] (SD)	87(32)	98 (39)	97 (31)	0.473
Dose reduction of neurotoxic chemotherapy				0.193
Yes	8 (32%)	10 (40%)	6 (35%)	
No	17 (68%)	15 (60%)	11 (65%)	
BMI at baseline				
Median (range)	24.2 (19–36)	25.8 (19–35)	23.7 (17–31)	0.215
< 20	1 (4%)	2 (8%)	2 (12%)	
20–25	14 (56%)	15 (60%)	10 (59%)	

(Continued)

TABLE 1 (Continued)

	HTEMS *n* = 25	TENS *n* = 25	Controls *n* = 17	*p*- value
> 25	10 (40%)	8 (32%)	5 (29%)	
Variation of BMI during neurotoxic chemotherapy [mean] (SD)	−1.9 (7.1)	−2.0 (6.7)	−2,8 (7.3)	0.230
Increase	10 (40%)	11 (44%)	5 (30%)	
Loss ≤10%	12 (48%)	10 (40%)	8 (47%)	
Loss of ≥10%	3 (12%)	4 (16%)	4 (23%)	
Known Diabetes/Pre-Diabetes (y/n)				0.180
Diabetes	6 (24%)	4 (16%)	7 (41%)	
No diabetes	19 (76%)	21 (84%)	10 (59%)	
Therapy during electrotherapy				
Yes	15 (60%)	14 (56%)	13 (77%)	
No	10 (40%)	11 (44%)	4 (23%)	
Chemotherapy†	6 (24%)	2 (8%)	7 (41%)	
Chemotherapy† and targeted therapy or immunotherapy	4 (16%)	4 (16%)	3 (18%)	
Endocrine therapy	2 (8%)	2 (8%)	1 (6%)	
Targeted therapy ± endocrine therapy	3 (12%)	6 (24%)	2 (12%)	

AJCC, American Joint Committee on Cancer; BMI, body mass index; HTEMS, high tone external muscle stimulation; TENS, transcutaneous electrical nerve stimulation; SD, standard deviation; * stratification factor for both intervention groups; # significant baseline differences between the control and the intervention groups; †Non-neurotoxic chemotherapies only were allowed (e.g. capecitabine, 5-fluorouracil, and irinotecan etc).

TABLE 2 EORTC QLQ CIPN20.

	HTEMS *n* = 25			TENS *n* = 25			Controls (CON) *n* = 17			
	T0	T1	Δ (CI)	T0	T1	Δ (CI)	T0	T1	Δ (CI)	Between group differences[1]
Sensory scale	45.0 ± 21.2	32.7 ± 15.4	−12.3** $^{d=1.4}$ (−19.6; −5.0)	47.3 ± 17.5	32.6 ± 17.7	−14.7*** $^{d=1.8}$ (−21.5; −7.8)	36.4 ± 21.7	33.2 ± 22.4	−3.3 (−9.7; 3.1)	TENS vs. CON $p = 0.0204$; HTEMS vs. CON $p = 0.039$ TENS vs. HTEMS $p = 1.0$
Motor scale	32.4 ± 18.2	24.2 ± 15.7	−8.2* $^{d=1.3}$ (−13.5; −2.6)	25.9 ± 20.6	17.7 ± 17.3	−8.2* $^{d=1.3}$ (−13.7; −2.7)	29.4 ± 22.7	26.6 ± 24.7	−2.8 (−7.9; 2.3)	TENS vs. CON $p = 1.0$ HTEMS vs. CON $p = 0.726$; TENS vs. HTEMS $p = 1.0$
Autonomic scale	10.0 ± 12.7$^{\$\$}$	10.7 ± 12.6	0.7 (−4.8; 6.1)	27.3 ± 25.9$^{\$\$}$	22.7 ± 24.9	−4.7 (−14.7; 5.4)	27.5 ± 31.7	27.5 ± 26.3	0.0 (−9.6; 9.6)	

Significant different baseline values compared to HTEMS $$ $p < 0.01$; significant within group differences ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; 1 Mann–Whitney-U-Test, d Cohan's d for effect size.

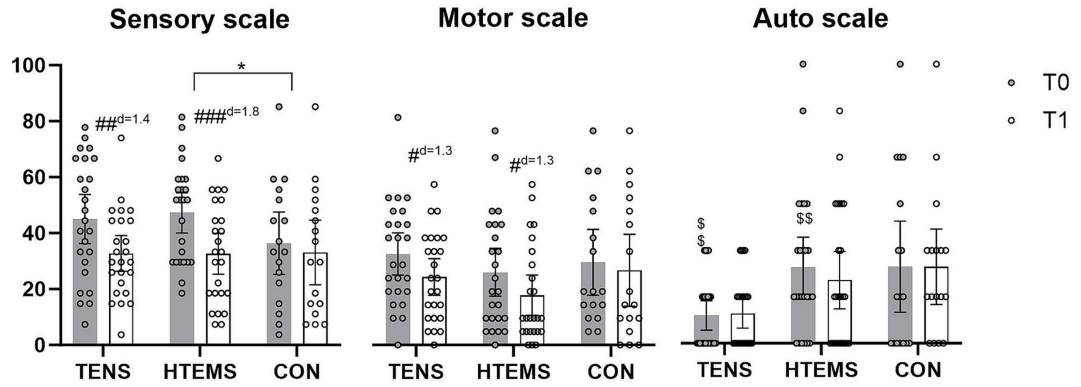

FIGURE 2
EORTC-QLQ-CIPN20 questionnaires before (T0, gray) and after (T1, white) the intervention in the transcutaneous electrical nerve stimulation (TENS), the high-tone external muscle stimulation (HTEMS) and the control (CON) groups, respectively. Significant within group differences: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$; significant between group differences: * $p < 0.05$; significant baseline differences: $$ $p < 0.01$; d: effect size Cohan's d. Values are presented as means and 95% confidence intervals with plotted individual values.

3.1 Feasibility

Eight patients (16%; 3 in the HTEMS group and 5 in the TENS group) reported adverse events related to the therapy. Two patients in the HTEMS group complained about pain caused by too high intensity and one reported an increase of symptom intensity. Three patients of the TENS group reported that the electrodes were overly adhesive, one patient complained about an increase of symptom intensity and for one patient the electrodes could not be ideally fixed on the skin. There was no difference in therapy compliance between TENS and HTEMS groups. Eighty-eight percent of patients randomized to HTEMS and 80% of patients randomized to TENS patients fulfilled the minimal duration of electrical therapy (≥ 1,200 min).

3.2 Primary endpoint

The primary endpoint for this study were changes in the EORTC-QLQ-CIPN20 questionnaire. Values of patients in the TENS and HTEMS groups improved significantly in the sensory (TENS: −12.3 ± 17.7, $p = 0.006$; HTEMS: −14.7 ± 16.5, $p < 0.001$) and motor scale (TENS: −8.2 ± 12.9, $p = 0.012$; HTEMS; −8.2 ± 13.4, $p = 0.015$), but not for the autonomic scale (Figure 2; Supplementary Table S2). There were no significant changes in the control group for any scale (sensory scale: −3.3 ± 12.4, $p = 0.294$, motor scale: −2.8 ± 10.0, $p = 0.264$ autonomic scale: 0.0 ± 18.6, $p = 1.000$). According to the Kurskal-Wallis test the groups differed significantly when comparing pre-post differences in the sensory scale ($p = 0.048$). By performing pairwise comparisons post-hoc, there were significant differences between the HTEMS and control group ($p = 0.039$). There were no further between group differences (Figure 2; Table 2).

3.3 Secondary endpoints

All secondary endpoints were analyzed after the per protocol principle. Twenty, 22 and 17 patients completed the EORTC-QLQ-C30 questionnaire in the TENS, the HTEMS and the control groups, respectively. Results of the EORTC-QLQ-C30 questionnaire are presented in Tables 3, 4. There was a tendency for an increase in the global health status (+8.7 ± 15.7, $p = 0.054$) and a significant improvement for physical functioning (7.9 ± 11.8, $p = 0.018$) from T0 to T1 in the HTEMS group only (Table 3). There were no further within group differences. Pre-post differences did not differ between groups in any variable (Tables 3, 4).

There were significant improvements in the CIPN grading according to CTCAE v4 from T0 to T1 in both intervention groups (TENS: from 3 to 1, $p = 0.004$; HTEMS from 2 to 1, $p = 0.012$) with no between group differences (Supplementary Figure S3). There were no within or between group differences in any clinical assessment (Supplementary Tables S2–S4).

4 Discussion

In cancer patients, peripheral neuropathic disorders often occur after the application of certain cytotoxic drugs, especially after taxanes and platinum salts (5). Patients are particularly affected by impairments in sensory functions, e.g., with tingling and numbness of the feet and fingers, which can be still present years after completion of chemotherapy (28, 29). After 8 weeks of home-based electrotherapy, our study showed a significant improvement in sensory and motor functions (Figure 2; Table 2). The CIPN grade according to CTCAE v4 also improved significantly in the TENS group from grade 3 (restricted basic functions; e.g. dressing and personal hygiene) to grade 1 (loss of deep tendon reflexes or paresthesia) and in the HTEMS group from grade 2 (impaired functional tasks; e.g. preparing food or housekeeping) to grade 1 (Figure 3; Supplementary Table S1). These changes are clinically relevant and have a direct impact on the everyday skills of affected patients.

At baseline, patients in our study showed considerably compromised sensory functions according to the EORTC-QLQ-CIPN20 questionnaire (TENS: 45/100, HTEMS: 47/100, CON: 36/100). Eight weeks of electrical therapy led to a significant relief of

TABLE 3 EORTC QLQ C30 symptom scales.

	TENS (n = 20)			HTEMS (n = 22)			Controls (n = 17)		
Symptom scales	T0	T1	Δ (CI)	T0	T1	Δ (CI)	T0	T1	Δ (CI)
Fatigue	38.9 ± 29.8	37.2 ± 31.7	−1.7 (−13.7;10.4)	43.3 ± 37.1	35.4 ± 29.6	−8.1 (−18.3;2.1)	52.3 ± 26.3	46.4 ± 28.1	−5.9 (−18.8;7.1)
Pain	38.3 ± 33.4	20.8 ± 31.0	−17.5 (−32.8;-2.2)	30.3 ± 36.6	24.2 ± 29.0	−6.1 (−15.6;3.5)	26.5 ± 20.5	25.5 ± 28.9	−1.0 (−17.2;15.2)
Nausea and vomiting	3.3 ± 6.8	5.0 ± 10.9	1.7 (−2.6;6.0)	9.1 ± 24.0	7.5 ± 18.3	−1.5 (−5.4;2.4)	12.7 ± 25.4	8.8 ± 18.7	−3.9 (−15.9;8.0)
Dyspnoea	10.0 ± 15.7	10.0 ± 21.9	0.0 (−11.3;11.3)	13.6 ± 28.5	15.2 ± 26.7	1.5 (−7.0;10.0)	27.5 ± 29.4	23.5 ± 25.7	−3.9 (−15.9;8.0)
Insomnia	30.0 ± 35.7	33.3 ± 37.5	3.3 (−9.0:15.6)	39.4 ± 40.7	27.3 ± 31.9	−12.1 (−31.8;7.5)	41.2 ± 34.4	35.3 ± 27.6	−5.9 (−22.2;10.4)
Appetite loss	16.7 ± 27.6	16.7 ± 29.6	0.0 (−7.2;7.2)	27.3 ± 39.4	22.7 ± 33.2	−4.5 (−27.7;4.2)	35.3 ± 41.6	23.5 ± 32.8	−11.8 (−27.4;4.2)
Constipation	20.0 ± 31.3	11.7 ± 24.8	−8.3 (−18.3;1.6)	9.1 ± 25.6	6.1 ± 19.6	−3.0 (−7.4;1.3)	19.6 ± 29	13.7 ± 23.7	−5.9 (−16.8;5.0)
Diarrhea	15.0 ± 29.6	15.0 ± 27.5	0.0 (−14.3;14.3)	19.7 ± 32.0	7.6 ± 22.8	−12.1 (−25.5;1.2)	39.2 ± 31.7	23.5 ± 36.8	−15.7 (−31.9;0.5)
Financial difficulties	11.7 ± 24.8	5.0 ± 16.3	−6.7 (−17.5;4.2)	15.2 ± 28.6	10.6 ± 26.0	−4.5 (−9.7;0.64)	17.6 ± 23.9	17.6 ± 23.9	0.0 (−8.6;8.6)

HTEMS, high tone external muscle stimulation; TENS, transcutaneous electrical nerve stimulation.

TABLE 4 EORTC QLQ C30 global health status and functional scales.

	TENS (n = 20)			HTEMS (n = 22)			Controls (n = 17)			
	T0	T1	Δ (CI)	T0	T1	Δ (CI)	T0	T1	Δ (CI)	Between group differences[1]
Global health status	55.8 ± 24.0	62.9 ± 20.9	7.1 (−3,1;17.2)	52.3 ± 13.7	61.0 ± 17.7	8.7 (1.7;15.7)	61.3 ± 17.4	60.8 ± 22.6	−0.5 (−12.6;11.6)	
Physical functioning	72.7 ± 20.5	77.0 ± 22.8	4.3 (−2.4;11.1)	72.7 ± 24.8	80.6 ± 20.9	7.9[2]*[r = 0.6] (2.7;13.1)	68.2 ± 22.9	67.8 ± 20.2	−0.4 (10.3;9.6)	HTEMS vs. CON p = 0.432 HTEMS vs. TENS p = 1.000
Role functioning	59.2 ± 23.7	64.2 ± 29.3	5.0 (−8.9;18.9)	59.1 ± 37.7	68.2 ± 30.4	9.1 (−7.0;25.2)	50.0 ± 26.4	58.8 ± 32.3	8.8 (−6.4;24.0)	
Emotional functioning	78.8 ± 21.5	80.8 ± 20.1	2.1 (−7.1;11.3)	67.0 ± 26.7	75.0 ± 20.1	8.0 (−1.3;17.2)	60.3 ± 25.3	65.2 ± 29.8	4.9 (−6.8;16.6)	
Cognitive functioning	80.0 ± 27.4	80.1 ± 21.1	0.8 (−8.5;10.1)	81.8 ± 27.2	81.1 ± 27.4	−0.8 (−8.1;6.6)	65.7 ± 34.6	70.6 ± 22.5	4.9 (−5.9;15.7)	
Social functioning	69.2 ± 29.3	77.5 ± 22.5	8.3 (−3.9;20.6)	63.6 ± 34.4	70.5 ± 27.7	6.8 (−5.2;18.8)	63.7 ± 27.8	70.6 ± 24.0	6.9 (−7.4;21.1)	

Significant within group difference *$p < 0.05$; [1]Mann–Whitney-U-Test; [2]Wilkoxon-Test; [r]Pearson's r as effect size.

−12 points (38%) after TENS and − 15 points (45%) after HTEMS therapy, compared to the control group (−3 points, 10%). These improvements were far beyond the minimal clinical important difference of 5.9 points defined by Yeo et al. (22) and did not differ between the two intervention groups. However, only the pre-post changes between HTEMS and the control group differed statistically significantly. A comparison with previous research in electrotherapy as treatment for CIPN is challenging, since the few existing studies are very heterogeneous regarding the population, outcome measures and treatment delivery. One study, where patients received TENS therapy during chemotherapy, reported no beneficial effects (30) while improvements of 10–20% in sensory symptoms were observed by

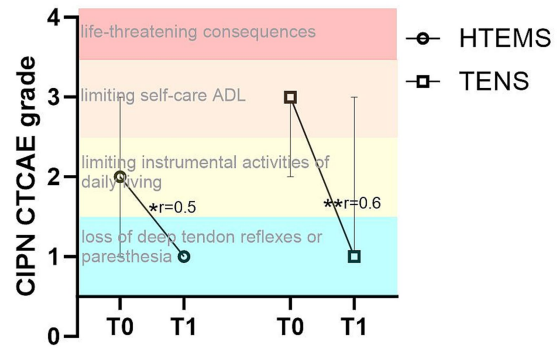

FIGURE 3
Chemotherapy-induced polyneuropathy (CIPN) grade according to CTCAE v 4 in the transcutaneous electrical nerve stimulation (TENS) and the high-tone external muscle stimulation (HTEMS) groups at baseline (T0) and after the intervention (T1). ADL: Activities of daily living; significant within group differences: ** $p < 0.01$, * $p < 0.05$; r: effect size Pearson's r; values are presented as median and 95% confidence intervals.

other authors when TENS was performed at least 3 months after stopping chemotherapy (14, 31, 32).

Deterioration of sensory and motor functions after chemotherapy are associated with reduced quality of life and a lower global health status (e.g., according to the EORTC-QLQ-C30), which worsens with symptom intensity (28, 33). A tendency for an increase in the global health status and an improvement for physical functioning after HTEMS were observed in our study. It is nevertheless surprising that the meaningful improvements of sensory impairments after HTEMS in our population were not reflected by clearer increases in quality-of-life domains or the global health status.

Short and easy to perform questionnaires like the CTCAE v4 to assess the CIPN grade are important in clinical routine. This questionnaire includes the limitations of the activities of daily living, is strongly correlated with the EORTC-QLQ-CIPN20 scores and shows a good convergent validity with the EORTC-QLQ-CIPN20 questionnaire (23). After 8 weeks of electrotherapy patients showed a significantly lower CIPN grading in the CTCAE v4 with no differences between intervention groups. However, it should be noted that the improvements after the CTCAE v4 questionnaire have to be viewed with caution since this data was not collected in the control group. Longitudinal studies assessing the course of CIPN show an increase of the incidence of CTCAE grade ≥ 1 and sensory impairments together with successive worsening of symptoms up to 1 year after chemotherapy (34). Spontaneous improvements in sensory impairments or the CTCAE grading without intervention seem therefore unlikely and emphasize the found effects of electrotherapy in our study.

Interestingly, we did not observe changes in any clinical assessment (e.g., cold/warm sensibility, reflexes, tuning fork test, etc.; see Supplementary Tables S2–S4). This is in line with other research reporting only slight changes in quantitative sensory parameters after exercise programs (35). The difference between clinically relevant improvements in CIPN scores vs. the lack of objective improvements by clinical examinations remains to be explained. Insensitivity of clinical evaluations regarding individual neuropathic symptoms but their interplay toward reduced complex neurological functions might be one explanation. Assessments that relate more to daily life activities, like closing buttons or walking on an uneven surface, may be more relevant for patients and may better illustrate impaired sensory and motor functions. Similarly, it is well-known that even relevant differences in specific adverse events of anticancer therapies like nausea or diarrhea do not always cause differences in quality of life in clinical trial patients (36).

4.1 Limitations and strengths

When interpreting the results of this study, some limitations have to be considered. One limitation is the decision not to implement a placebo group. The selected intensity of electrotherapy should produce muscle contractions, which would not be achievable using a placebo device. It is therefore possible that patient reported outcomes were biased by the placebo effect. Another limitation is the retrospective recruitment of the control group, which occurred approximately 7 months after the original study protocol. This group was not stratified according to the neurotoxic agent, causing a slight imbalance in the use of platinum compared to the randomized groups, and only completed the EORTC-QLQ-CIPN 20 and C30 questionnaires. The retrospective nature of the control group is a major limitation of our study, but supports the improvements of the sensory scale, especially after HTEMS. Increases in the CTCAE grading after electrotherapy on the other hand, must be interpreted with caution. Deviating from the original study protocol, patients were included with a CIPN grade ≥ 1 according to CTCAE v4. This is in contrast with other research where only patients with CIPN grade ≥ 2 were included. However, despite this difference in the inclusion criteria, patients in our study showed remarkable impairments of sensory and motor functions at baseline measured with the EORTC-QLQ-CIPN20 questionnaire. Finally, ongoing chemotherapy is potential confounder in our trial, since it could have weakened the effect of electrotherapy. Self-evidently, only non-neurotoxic chemotherapies were allowed and the number of patients who received further chemotherapy did not differ between the two groups. As ongoing treatments are common in oncology, prohibiting additional therapies would have not accurately reflected real-world practice. One of the strengths of this clinical trial was - aside from the prospective design and the randomization - the home-based intervention approach. After one extensive training session, patients were able to perform the electrotherapy independently. The treatment was easy and quick to comprehend and travel to a therapy center was not necessary. This was mirrored by a good acceptance and compliance (read from the records of the devices) of 88% (HTEMS) and 80% (TENS). The electrotherapy procedures could be performed safely and there were only a few (16%) unpleasant side effects such as pain caused by too high intensity or discomfort caused by overly adhesive electrodes.

5 Conclusion

Electrotherapy, especially the HTEMS intervention, seems to be a successful treatment strategy to mitigate the impairment of sensory functions in CIPN patients. Further investigation is necessary to explore the impact of electrotherapy on everyday tasks and activities. Using a larger sample size and a multicenter approach, the influence of different neurotoxic agents on TENS and HTEMS therapy effects

could also be clarified. Although more studies are desirable, HTEMS and TENS can be considered as treatment options for CIPN after completion of neurotoxic chemotherapy since they are easy to administer and have negligible side effects.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics committee of Salzburg County. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RS: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Supervision. SG: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. FR: Writing – original draft, Writing – review & editing, Formal analysis, Methodology, Visualization. TJ: Conceptualization, Data curation, Funding acquisition, Methodology, Validation, Writing – original draft, Writing – review & editing. GR: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. VC: Data curation, Writing – original draft, Writing – review & editing. KL: Investigation, Writing – original draft, Writing – review & editing. JH: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. YK: Writing – original draft, Writing – review & editing. MF: Conceptualization, Resources, Writing – original draft, Writing – review & editing. DS-S: Conceptualization, Funding acquisition, Supervision, Validation, Writing – original draft, Writing – review & editing. RG: Conceptualization, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

SG receives honoraria from MSD, Novartis, Astra Zeneca, Eli Lilly, Seagen Daiichi Sankyo Europe GmbH and Gilead Sciences and has a consulting role for these companies and Stemline Therapeutics. The institution of SG receives funding (for projects not related to this paper) and travel expenses from Roche, Daiichi Sankyo Europe GmbH, Novartis, Pfizer, Caris Life Sciences, Eli Lilly, Seagen, Gilead Sciences, Janssen and AstraZeneca. GR receives honoraria from Amgen, AstraZeneca, Daiichi Sankyo GmBH, Eli Lilly, Gilead Sciences, MSD, Novartis, Seagen, Stemline Therapeutics, Roche and BMS and has a consulting role for these companies and Pfizer. RG holds a stock in Novo Nordisk and Eli Lilly and receives honoraria from Celgene, Roche, Merck, Takeda, AstraZeneca Novartis, Amgen, BMS, MSD, Sandoz and Abbvie. RG also is consultant for Celgene, Novartis, Roche, BMS, Takeda, Abbvie, Astra Zeneca, Janssen, MSD and Amgen and expert testimony for Roche, Amgen, Janssen, Astra Zeneca Novartis, MSD, Celgene, Gilead Sciences and BMS. RG receives funding for projects not related to this paper from Celgene, Roche, Merck, Takeda, AstraZeneca Novartis, Amgen, BMS, MSD, Sandoz and Abbvie.

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Supplementary material

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Neuropsychological outcome of indoor rehabilitation in post-COVID-19 condition—results of the PoCoRe study

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Background: Post COVID-19 condition (PCC) is increasingly recognized as a debilitating condition characterized by persistent symptoms following SARS-CoV-2 infection. Neuropsychological deficits, including cognitive impairments and fatigue, are prevalent in individuals with PCC. The PoCoRe study aimed to evaluate the burden of neuropsychological deficits in PCC patients undergoing multidisciplinary indoor rehabilitation and to describe possible changes in this symptomatology.

Methods: The PoCoRe study, a prospective, non-randomized, controlled longitudinal study, recruited PCC patients from six German indoor rehabilitation centers. Eligible participants underwent comprehensive neuropsychological assessments at admission and discharge. Various measures were employed, including the fatigue scale for motor functioning and cognition (FSMC), the Test Battery for Attention (TAP) and the Montreal Cognitive Assessment (MoCA).

Results: Out of the 1,086 recruited participants, a total of N = 701 participants were included in the main data analysis. The prevalence of fatigue on admission was high (84.6%) and decreased significantly by discharge (77.4%), with a mild effect size. Reaction times on the alertness subtest were abnormal in 70% of patients on admission and 50% on discharge. Sustained attention was abnormal in 55% of patients on admission, decreasing to 43% on discharge. These differences were significant with mild effect sizes. Furthermore, of the 27% of participants with pathological MoCA scores at admission, 63% improved to normative levels during rehabilitation, indicating a significant treatment effect ($p \leq 0.001$). However, the MoCA demonstrated limited sensitivity in detecting attention deficits.

Conclusion: The PoCoRe study highlights the high prevalence of neuropsychological deficits and fatigue in PCC patients, with notable improvements observed following multidisciplinary rehabilitation. Challenges remain in accurately identifying and addressing these deficits, underscoring the importance of comprehensive neuropsychological assessment and tailored rehabilitation interventions. Further research is warranted to optimize

screening tools and enhance neuropsychological care for PCC patients in both rehabilitation and outpatient settings.

KEYWORDS

post COVID condition (PCC), neurologic rehabilitation, neuropsychology, fatigue, Montreal Cognitive Assessment (MoCA)

Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has left an indelible mark on global health, society, and economies. While much attention has rightfully focused on acute illness and preventive measures, the aftermath of the virus is increasingly coming to light. Among the emerging concerns is the phenomenon known as Post COVID-19 condition (PCC).

PCC occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis (1).

At least 65 million people worldwide are estimated to have PCC (2).

The most prevalent PCC symptoms two-years after SARS-CoV-2 infection are fatigue and cognitive impairments (3–5). In a comprehensive neuropsychological evaluation patients with PCC showed significantly lower scores in domains of memory, language, processing speed, visuospatial function, executive function, and higher depressive and anxiety symptoms (6).

Recognizing the urgent need for targeted interventions to address the complex sequelae of PCC, the PoCoRe study was initiated as a collaborative effort across six German indoor rehabilitation centers specializing in neurologic or psychosomatic care. The centers adopted their therapeutic concept to the specific needs of the PCC patients (7).

The present study aims to elucidate the symptom burden of neuropsychological deficits in individuals grappling with PCC while also evaluating the efficacy of a multidisciplinary indoor rehabilitation program in ameliorating these challenges. By systematically assessing cognitive function, and functional outcomes before and after rehabilitation, this research aims to contribute valuable insights into the long-term management of PCC and inform the development of targeted interventions to support affected individuals on their path to recovery.

Methods

The PoCoRe study is a prospective, non-randomized, controlled longitudinal study in Germany. A study protocol has been published previously (7).

The study took place in six indoor rehabilitation clinics specialized in neurological rehab and psychosomatic rehab. It was funded by the German pension found (Deutsche Rentenversicherung), so insured persons could take part from March 2022 to December 2023. All consecutively admitted rehabilitation patients who started rehabilitation as a result of PCC and who met the eligibility criteria as well as consent to participate in the study were included.

Eligibility criteria

- SARS-CoV-2-infection and following PCC: Complaints that are still present more than 12 weeks after the onset of SARS-CoV-2 infection and cannot be explained otherwise.
- As a consequence of PCC at the time of the start of rehabilitation the presence of functional limitations that may threaten the ability to work.
- Written informed consent to participate in the study.
- Aged 18 years or above.
- Sufficient knowledge of the German language to participate in the study.
- Patients with ME/CFS were not excluded. However, we did not assess ME/CFS symptoms systematically within our study design.

Interventions

The clinics and their treatment programs are reported previously (7). The specializations diverge in the duration and frequency of the therapies, but uniformly cover all essential symptom areas of the PCC with corresponding offers (psychoeducation, exercise, psychotherapy, pacing, breathing and relaxation therapy, cognitive training). Within in this framework, the treatment program was adapted to the individual needs of the patient, including adaptations for individuals affected by ME/CFS (see Supplementary Table 1 for comprehensive information).

Study variables

Trained psychologists conducted the study-related examinations/tests on admission to rehabilitation and on discharge. The participants completed the questionnaires autonomously (for a full listing of the questionnaires used, see the study protocol) (7).

Measures/outcomes

Neuropsychology

Montreal cognitive assessment

The MoCa is a cognitive screening instrument. It is performed by healthcare professionals to detect early stages of dementia and mild cognitive impairment. It includes subtests for various cognitive abilities such as memory, language, contextual thinking, attention and concentration, behavior, arithmetic, temporal and spatial orientation and the ability to recognize complex shapes and patterns, while also taking into account educational background by awarding an extra point if they have not completed at least 12 years of education. Scores

of 26 to 30 points are considered unremarkable, no limitations, 6 to 25 points indicate at least mild cognitive impairment, and 0 to 5 points are interpreted as extreme mental impairment (8).

TAP-test

The Test Battery for Attention (TAP) is a software package that offers a collection of different tests that can be used to measure the various aspects of attention in a differentiated way and also cover related aspects of visual perception. Used subtests are alertness, working memory, sustained attention, and divided attention. The battery we chose took about 45 min to complete (9) (see Table 1). Detailed information on the TAP is openly available openly available at https://www.psytest.net/en/test-batteries/tap/subtests.

Assessment of fatigue

Fatigue scale for motor functioning and cognition (FSMC)

The FSMC is a self-rating scale for assessment of subjective symptoms of fatigue and provides a differential quantification and grading of cognitive and motor fatigue. The FSMC was tested against several external criteria (e.g., cognition, motivation, personality and other fatigue scales) and provides satisfactory results with regard to the test quality criteria. Twenty items (10 for motor fatigue, 10 for cognitive fatigue) are rated using a five-point scale (strongly disagree to strongly agree) (10).

Data management and analysis

The above outcomes were assessed by patient questionnaires (FSMC, MoCA) and cognitive assessment (TAP) or extracted from rehabilitation discharge letters (e.g., primary and demographic data; socio-medical data). For more information on the full assessment included in the PoCoRe study, we have uploaded in Supplementary Table 2. If participants withdrew informed consent, the collected data was deleted. The patient data were stored anonymously in an electronic study-data file with a patient cipher, whereby the paper–pencil data were entered in an automated conversion procedure and partly manually. Paper-pencil questionnaires were stored in locked filing cabinets and electronic data were stored on secure servers. To ensure a safe and secure environment for the data collected, data transmission was encrypted using Secure Socket Layer (SSL) technology.

TABLE 1 Overview of the TAP subtests used.

Subtest	Cognitive domain	Information about
Alertness	Intensity of attention	Basal reactivity, general processing speed, reaction stability, distinction tonic alertness
Working memory	Executive functions, control of the focus of attention	Ability to continuously update the content of working memory
Sustained attention	Intensity of attention	Longer-term maintenance of attention with high target stimulus density
Divided attention	Attentional selectivity, focused attention, visuo-spatial attention	Ability to focus attention on two tasks simultaneously

Statistical methods

Statistical analyses was conducted using R version 4.3.0 (9), including the stats package, and ggplot2 package (11). Descriptive analyses were performed concerning FSMC, TAP tests, MoCA and sociodemographic data. Indoor rehabilitation effects were calculated employing the Wilcoxon signed-rank test for FSMC and ANOVA for TAP test and MoCA. p-values were set to <0.05 and adjusted using the Bonferroni-Holmes method. For Wilcoxon Signed Rank Tests, the effect size r was calculated using the following formula: $r = z/\text{sqrt}(N)$ (12).

In addition, sensitivity and specificity of the MoCA predicting results of the alertness testing was evaluated (13).

Ethics and study registration

All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the responsible ethics committees [reference numbers: University Hospital Regensburg (including Berlin and Gelderland Klinik): Z-2022-1749-8; Westerwaldklinik: Landesärztekammer Rheinland Pfalz: 2022–16,395; Konstanz and Gailingen: University of Constance 25/2022; Todtmoos: Landesärtzekammer Baden-Württemberg: B-F-2022-032]. The PoCoRe study was registered 03 February 2022 at https://studienanmeldung.zks-regensburg.de.

Results

Out of the 1,086 recruited participants, a total of $N = 701$ participants were included into data analysis, based on having complete data in the alertness subtest of the TAP (admission and discharge). They had a mean age of 49.5 years (range: 21 to 65, SD = 10.10) and 70.9% were female. The initial infection occurred on average 29 months ago (range: 9 to 50, SD = 8.11).

There was no significant difference concerning age, FSMC values and TAP values on admission between the completed sample and the dropouts at discharge. Because of violated assumptions for parametric testing, the non-parametric Mann–Whitney U test was used to compare MoCA scores at admission. There was a statistically significant difference (U = 79913.00, $p = 0.003$) in MoCA scores between the completed sample (M = 26.53, SD = 2.61) and the dropout sample (M = 25.82, SD = 3.54) with a small effect size of r = 0.10. Within the complete sample, 177 out of 657 individuals (27%) showed a MoCA score below cut-off (<26). This proportion is significantly different from the 105 out of 277 individuals (38%) within the dropouts (Chi-squared = 10.602, df = 1, $p = 0.0001$).

Prevalence of Fatigue on admission was high, to discharge it decreased significantly with a mild effect size (see Table 2).

The results of the TAP subtests were converted to T values. T values lower than 40 were considered to be abnormal (14).

The reaction times of the alertness subtest scored abnormal in 70% of patients on admission and 50% on discharge (see Figure 1).

Sustained attention (depicted as the number of omitted answers) was abnormal in 55% on admission with a decrease to 43% on discharge. These differences were significant with mild effect sizes (see Figure 1).

Working memory was impaired in 26% at baseline and 20% at discharge. A significant and mild effect (see Figure 1).

Divided attention scored abnormal in 33% on admission with a decrease to 26% on discharge: a significant and small effect, too (see Figure 1).

The treatment effects for sustained attention, working memory and divided attention were even larger when we took only those participants into account scoring with abnormal results on admission with a T < 40 (see Table 2).

To evaluate the clinical relevance of the observed group-level improvements, we additionally calculated the proportion of individuals who improved on a clinically relevant level, according to critical differences in T-values (T_{diff}) provided within the manual of the TAP (14).

At discharge, 37 participants (5.4%) showed clinically relevant improvements in working memory compared to admission ($T_{diff} \geq 14.079$), while 10 participants (1.5%) showed clinically relevant worsening. In divided attention, 98 participants (15.1%) showed clinically relevant improvements ($T_{diff} \geq 13.060$), while 32 participants (4.9%) showed clinically relevant worsening. In sustained attention, 119 participants (17.9%) showed clinically relevant improvements ($T_{diff} \geq 10.312$), while 52 participants (7.8%) showed clinically relevant worsening. At discharge, 341 participants (48.6%) showed clinically relevant improvements in alertness compared to admission ($T_{diff} \geq 3.791$), while 82 participants (11.7%) showed clinically relevant reductions in reaction times.

Improvements in alertness being the most prevalent finding on both the group and individual level, we performed further post-hoc analysis evaluating whether the patients significantly improving in alertness also significantly improve in fatigue measured by the difference in FSMC scores. As indicated by *Wilcoxon Signed Rank Tests*, patients who showed clinically relevant improvements in

TABLE 2 Prevalence of deficits and Wilcoxon signed rank test comparing TAP and fatigue measures at admission (T1) and discharge (T2).

	Prevalence of deficits (n_{def})		Mean (SD)		Median		*n*	*z*	*p*	p_{adj}	*r*
	T1	T2	T1	T2	T1	T2					
TAP measures											
Alertness	70.2% (492)	49.5% (347)	33.80 (10.38)	38.41 (11.23)	34	40	701	−13.13	< 0.001	< 0.001	**−0.50**
Working memory	25.6% (176)	19.5% (134)	45.68 (8.12)	47.45 (8.01)	48	48	686	−5.71	< 0.001	< 0.001	−0.22
Sustained attention	55.5% (371)	43.0% (291)	39.27 (10.89)	42.22 (11.44)	39	42	676	−7.96	< 0.001	< 0.001	**−0.31**
Divided attention	33.2% (224)	25.8% (171)	45.27 (12.44)	47.70 (12.47)	46	52	662	−5.27	< 0.001	< 0.001	−0.20
Deficit-subgroups TAP											
$Alertness_{def}$			28.42 (6.60)	34.96 (10.66)	29	36	492	−14.02	< 0.001	< 0.001	**−0.63**
$Working\ memory_{def}$			35.04 (2.84)	41.27 (7.52)	35	40	172	−9.22	< 0.001	< 0.001	**−0.70**
$Sustained\ attention_{def}$			31.35 (6.37)	36.51 (10.30)	34	37	358	−9.88	< 0.001	< 0.001	**−0.52**
$Divided\ attention_{def}$			30.80 (5.36)	38.69 (12.59)	31	37	213	−8.54	< 0.001	< 0.001	**−0.59**
Fatigue (FSMC)											
FSMC_total	84.6% (550)	77.4% (501)	76.86 (15.13)	73.56 (17.62)	80	77	647	−7.50	< 0.001	< 0.001	−0.29
FSMC_cognitive	77.7% (505)	71.7% (464)	38.68 (8.28)	37.08 (9.35)	40	39	647	−6.56	< 0.001	< 0.001	−0.26
FSMC_motor	83.4% (542)	77.0% (498)	38.18 (7.60)	36.48 (8.85)	39	38	647	−7.35	< 0.001	< 0.001	−0.29

TAP measures: Age-, gender-, and education-corrected T-scores at admission (T1) und discharge (T2). Cut-off value for deficits: T < 40. Alertness: Median of reaction times without warning signal. Working memory: number of omissions. Sustained attention: number of omissions. Devided attention: number of omissions. Deficit-subgroups TAP: We performed Wilcoxon-Signed-Rank-Tests for the subgroups containing the participants who showed deficits at T1 in the corresdponding TAP measure. Fatigue (FSMC): Sum scores are displayed; cut-off values for deficits correspond to severe fatigue: FSMC_total (>62), FSMC_cognitive (>33); FSMC_motor (>31). p_{adj} = *p*-values corrected for multiple testing, using Bonferroni-Holmes correction. *r* = effect size r (32), medium effect sizes are highlighted in bold, large effect sizes bold and underlined.

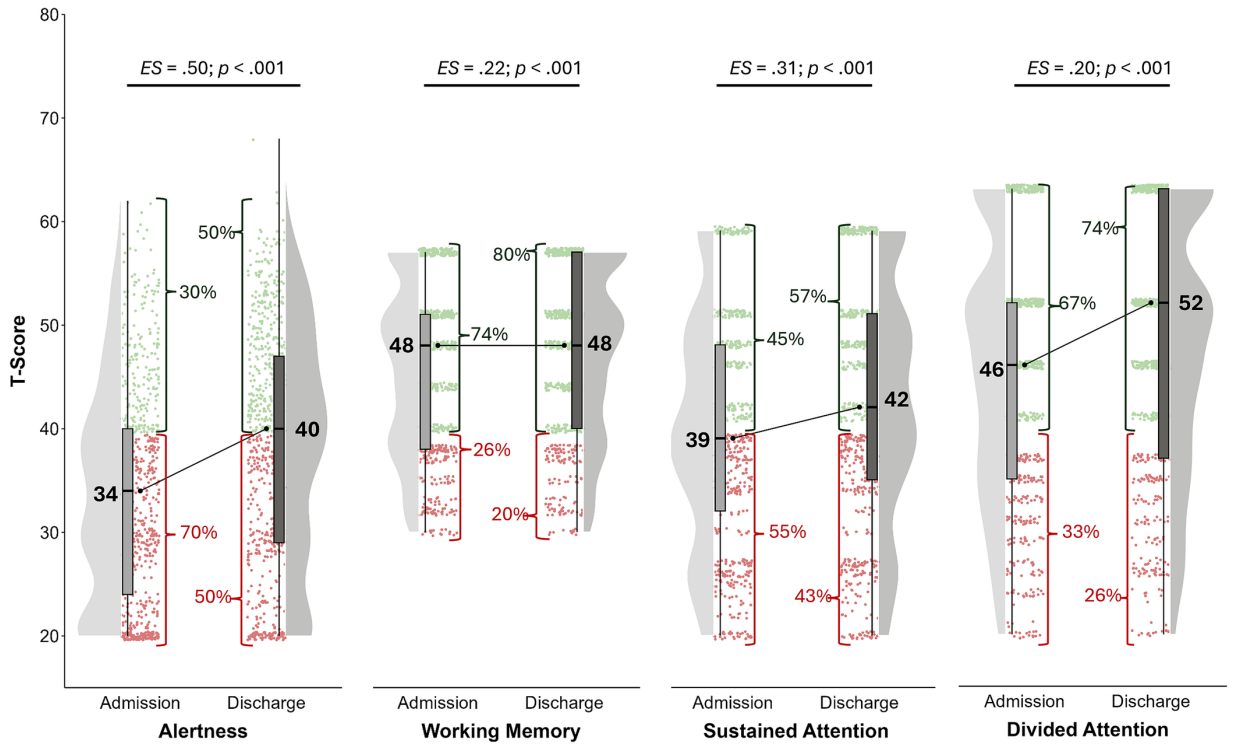

FIGURE 1
Age-, gender-, and education-corrected T-scores at admission (T1) und discharge (T2). Values in red represent impaired performance (T < 40), while green values are interpreted as at least average. Alertness: Median of reaction times without warning signal; n_{T1} = 701; n_{T2} = 701. Working memory: number of omissions; n_{T1} = 688; n_{T2} = 686. Sustained attention: number of omissions; n_{T1} = 681; n_{T2} = 676. Divided attention: number of omissions; n_{T1} = 674; n_{T2} = 662.

alertness showed higher improvements in overall fatigue and cognitive fatigue with small effect sizes, but no significant improvements in motor fatigue (see Table 3).

We pooled the FSMC and TAP data by assuming the presence of neurocognitive deficits in the attention domain if two subdomains of the TAP test scored T < 40. Based on this assumption, 54% of PCC patients with severe fatigue were found to have coexisting attentional disorders.

Applying the MoCA test at admission showed suspicious results (cut off <26) in 177 out of 657 individuals (27%) of the participants, which normalized in 72 out of 115 (63%) at follow-up on discharge (see Figure 2).

To detect clinically relevant changes in MoCA scores over time, Krishnan et al. (15) calculated a reliable change index (16) of ±1.73 based on a healthy sample. Within our sample, 68 of 115 (59%) impaired patients at T1 (cutoff <26) showed an improvement of at least 2 points on the MoCA score, while 3 of 115 (3%) participants showed a clinically relevant worsening of the MoCA score (≤ -2).

For the evaluation of the specificity and sensitivity of the MoCA to detect neurocognitive deficits in attention domain, we compared the prevalence of abnormal MoCA sum score at T1 with the prevalence of neurocognitive deficits in attention domain at T1. The ladder we defined as the prevalence of deficits as showing impairments in at least two domains of the TAP. It should be noted, that we included only participants with complete MoCA and TAP data at T1 (N = 875) for this subanalysis. The MoCA test has a specificity of 83% to predict a deficit in attention, but only a sensitivity of 37%.

Discussion

With the aim of assessing the prevalence of neuropsychological deficits in PCC and depicting potential changes throughout the course of indoor rehabilitation, we conducted a comprehensive, standardized assessment of attention at the beginning and end of a multidisciplinary rehabilitation program.

Performing subtests of the TAP, we measured a high prevalence of attention deficits, particularly in the domains alertness and sustained attention. Compared to admission, we found significant overall improvement in all subdomains at discharge, especially large effects among those admitted with impairments.

Our data adds to existing knowledge on overall cognitive slowing in post COVID patients (17), indicated by slow reaction times in alertness that were highly prevalent in our sample. Further, we provided evidence that a rehabilitation program can lead to improvements on a group level and clinically relevant individual improvements. On an individual level, we could show that patients with clinically relevant improvements in cognitive slowing were more likely to improve in overall and cognitive fatigue symptoms. While this effect was small, it adds to the findings on the interplay of cognitive slowing and fatigue symptoms.

Analyses on individual levels revealed that while a higher proportion of patients improve within the subtests of attention, some individuals (1.5–11.7%) show worse performance at discharge compared to admission. This proportion being rather small, this finding highlights the importance of individualized

TABLE 3 Wilcoxon signed rank test comparing changes in fatigue scores (T1-T2) for patients clinically improving ($A_{improve}$) and not improving ($A_{non-improve}$) in alertness.

	Mean (SD)		Median (*n*)		*z*	*p*	p_{adj}	*r*
	$A_{improve}$	$A_{non-improve}$	$A_{improve}$	$A_{non-improve}$				
Changes in fatigue (FSMC)								
FSMC_total_change	3.84 (13.76)	2.57 (9–31)	2.5	2.0	2.33	0.020	0.040	0.09
FSMC_cognitive_change	1.93 (7.24)	1.15 (5.09)	1.5	1.0	2.80	0.005	0.015	0.11
FSMC_motor_change	1.92 (7.12)	1.42 (4.81)	1.0	1.0	1.15	0.249	0.249	0.04

Patients with clinically relevant improvement ($A_{improve}$; $n_{improve}$ = 341) are identified by increases in alertness reaction times at discharge compared to admission (median without warning signal) by at least T = 3.791; patients with lower differences are part of the non-improvement group ($A_{non-improve}$; $n_{non-improve}$ = 360). Changes in Fatigue Scores are measured by the difference in the FSMC at admission (T1) and discharge (T2). p_{adj} = *p*-values corrected for multiple testing, using Bonferroni-Holmes correction. *r* = effect size r (12).

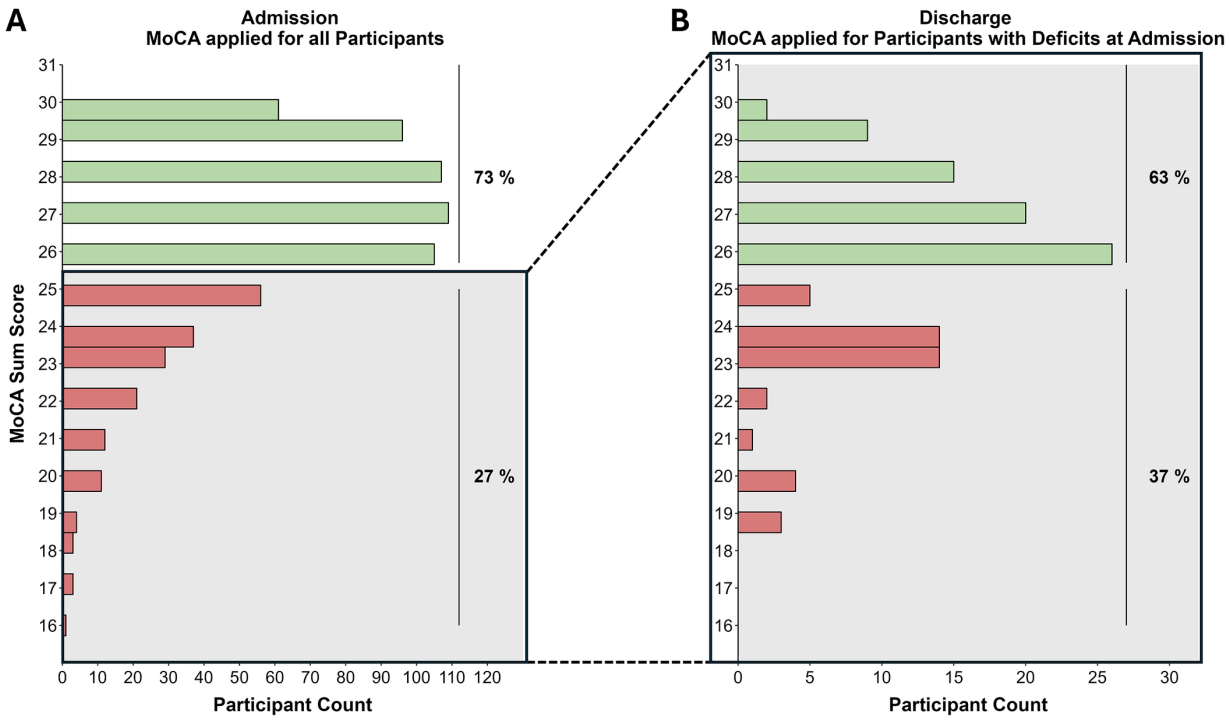

FIGURE 2
Distribution of MoCA sum scores at admission **(A)** and discharge **(B)**. Green bars indicate normative MoCA scores (≥26), red bars indicate deficits. **(A)** $n_{normative}$ = 480 (73%); $n_{impaired}$ = 177 (27%). **(B)** $n_{normative}$ = 72 (63%); $n_{impaired}$ = 43 (37%).

diagnostics, treatment plans, and evaluation, and might encourage further research to evaluate interventions on an individual basis in addition to group comparisons. This aligns with publications highlight the heterogeneity of the post COVID population and the need for comprehensive, interdisciplinary diagnostics and individualized treatment. This, however, acquires additional resources, as discussed by, e.g., Hayden (18).

Of the 27% of participants with suspicious scores on the MoCA at admission, 63% improved to a normative level during rehabilitation, also indicating a positive effect of the rehabilitation program in this subgroup. For the interpretation of this effect, it should be considered that we observed baseline differences in MoCA scores, with T2-dropouts showing lower performance than the analyzed complete sample. However, this group difference only had a small effect size (r = 0.10), suggesting a small potential bias.

The MoCA test did not prove effective as a screening tool for detecting attention deficits in the participating PCC patients. It was suspicious in only 27% of the cases, and thus only predicted the presence of attentional deficits (measured with the TAP) with a sensitivity of 37%.

Neuropsychological studies have found that the executive functions are particularly severely impaired in PCC patients (19).

Others emphasize the importance of attention deficits (20, 21). In addition to the findings of Ariza et al. (22), our data show the importance of conducting a differentiated test of attention.

It should be noted that the same version of the MoCA and TAP was applied at admission and discharge, so that learning effects cannot be ruled out. However, these could be minimal since several weeks lie between the measurement points (23).

Furthermore, assessment was only possible for deficits in the attention domain; other neurological subdomains of the MoCA (e.g., memory) were not extensively explored. Further investigations could explore whether adjusted cut-off values in the MoCA, combined with items from other questionnaires, offer a pragmatic screening alternative.

Fatigue has a very high prevalence and amount in our cohort.

This is interesting because between 6 and 24 months after infection, about half of all fatigue cases resolve in a population-based study (24). Therefore our PCC patient cohort is considered to be a selected population. Our PCC patients were on average 29 months post-infection and can be considered chronic patients. Despite such a high degree of chronicity, a substantial and significant effect of indoor rehabilitation was observed. To our knowledge, this is the first prospective study to demonstrate such effects in a large patient population with PCC.

However, the impact on fatigue symptoms was less pronounced compared to attention deficits. Consequently, the improvement in self-reported cognitive fatigue and measured cognitive performance does not appear to align within our sample. Additionally, our findings revealed that neurocognitive deficits in the attention domain (defined as deficits in at least two subdomains of attention, as measured by the TAP) coexist with severe fatigue (FSMC) in 54% of cases. This suggests a significant overlap between attention deficits and severe fatigue; however, attention deficits alone do not provide a complete explanation for the presence of fatigue in our sample.

Other studies have similarly discovered that self-reported fatigue measures do not always correlate with reaction times (25). This discrepancy may be due to the measurement of two distinct constructs: While the FSMC assesses perceived fatigue symptoms as a stable trait, the TAP measures cognitive performance as a state.

In this context, the question of the influence of psychological, respectively, psychosocial factors naturally arises. Numerous studies show a certain psychological predisposition for the onset of a PCC (26–28). This question was examined in detail in a subset at one of the participating centers of our PoCoRe study, and Kupferschmitt and colleagues were able to demonstrate a significant improvement in the PHQ-9 (a measure of depression) as a result of indoor rehabilitation treatment at one of the participating centers. However, this did not correlate with the measured changes in the neuropsychological assessment (29).

In a highly nuanced combination of neuropsychological tests and the Patient-Health- Questionnaire- 9 to assess depressive symptoms, Morawa and colleagues found frequently deficient neuropsychological parameters. Clinically relevant depressive symptoms were associated with an elevated risk for an impairment regarding some cognitive functions (30).

It should be noted, however, that the participating clinics also addressed the psychological aspects of rehabilitation needs and developed and evaluated their own cognitive behavioral therapy (CBT) procedures for this clientele (31).

Overall, our study shows desired rehabilitation effects, meaning improvement in the tested neuropsychological domains and fatigue at discharge compared to admission. One limitation is that we cannot generalize this statement to severely affected individuals, as our sample consisted of individuals with a sufficiently good overall health status to be eligible for rehabilitation, due to the German healthcare system regulations.

Another limitation of our study is the absence of a control group, which means we cannot ascertain whether the improvements observed are attributable solely to the rehabilitation program or could also be attributed to spontaneous remission. However, since the PCC patients had already experienced considerable chronification, spontaneous remission is unlikely to be the cause of these improvements.

Another limitation, however, is the considerable drop-out rate among participants for neuropsychological testing at the time of discharge. Since there were no significant differences between this group and the group of participants with a complete TAP examination when comparing FSMC values and TAP examination results at T1, we believe that our results are still representative. For the interpretation of the improvements in MoCA-Scores, it should be considered that we observed baseline differences in MoCA scores, with T2-dropouts showing lower performance than the analyzed complete sample. However, this group difference only had a small effect size ($r = 0.10$), suggesting a small potential bias. Still, potential training effects cannot be excluded.

The reasons for discontinuation were not exclusively due to the refusal of the rehabilitants to undergo a second TAP examination, but also were related to other reasons, for example expiration of funding commitments on the part of the payers or personal reasons that made it necessary to discontinue rehabilitation.

In the future, it seems desirable to combine the data collected here with further data on the psychological outcomes of the participants. In addition, the data indicate the need for intensive neuropsychological assessment and therapy as part of rehabilitation. The aftercare situation is particularly worrying as many as 50% of patients are discharged from rehabilitation with persistent neurocognitive deficits in the attention domain and were searching for further intensive neuropsychological training required. A catamnesis of the PoCoRe cohort 6 months after discharge from rehabilitation will show how the rehabilitation procedures and other contextual factors have affected quality of life and social and occupational participation.

Conclusion

In a large cohort we have shown the high prevalence of neuropsychological deficits and fatigue among PCC patients who generally benefited from indoor rehabilitation in specialized centers. Given the so far unresolved overlap with self-reported fatigue, depressive symptoms, and other factors such as sleep quality, a comprehensive neuropsychological assessment is essential for developing an individualized treatment plan. Screening instruments need to be evaluated carefully for adequate sensitivity. This underscores the need for improved neuropsychological care in both rehabilitation and outpatient settings.

Data availability statement

The datasets presented in this article are not readily available they are available on request and after verification. Requests to access the datasets should be directed to Thilo Hinterberger, Thilo.Hinterberger@ukr.de.

Ethics statement

The study was approved by the responsible ethics committees (reference numbers: University Hospital Regensburg (including Berlin and Gelderland Klinik): Z-2022-1749-8; Westerwaldklinik: Landesärztekammer Rheinland Pfalz: 2022–16,395; Konstanz and Gailingen: University of Constance 25/2022; Todtmoos: Landesärtzekammer Baden-Württemberg: B-F-2022-032). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. MT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CK: Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. CH: Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. SK: Data curation, Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. AK: Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. IM: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Software, Writing – original draft, Writing – review & editing. NW: Formal analysis, Writing – original draft, Writing – review & editing, Data curation. GS: Investigation, Writing – original draft, Writing – review & editing. TL: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. VK: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. TH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1486751/full#supplementary-material

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Effects of physiotherapy on degenerative cerebellar ataxia: a systematic review and meta-analysis

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Background: Evidence of the effectiveness of physiotherapy, including muscle strength training, coordination training, aerobic exercise, cycling regimen, balance training, gait training, and activity of daily living training, in patients with degenerative cerebellar ataxia (DCA) was insufficient for clinical decision making. We aimed to explore clinical outcomes and examine the parameters associated with physical impairment and activity in people with DCA based on preregistration (PROSPERO: CRD42024493883).

Methods: The PubMed, Cochrane Library, CHINAL, and PEDro databases were searched for relevant randomized controlled trials (RCTs). Data extraction, quality assessment, and heterogeneity analyses were conducted. The Grading of Recommendations Assessment, Development, and Evaluation framework (GRADE) was used to assess the quality of evidence, and a meta-analysis was performed.

Results: Eighteen RCTs, which included 398 participants, showed a serious risk of bias (RoB) and low certainty of evidence for this primary outcome. For meta-analysis, 315 patients assessed based on the Scale for Assessment and Rating of Ataxia (SARA) were included. Overall, physiotherapy significantly reduced SARA scores (MD = −1.41, [95% CI: −2.16, −0.66]); the subgroup analysis showed that the following interventions exerted significant effects: multi-aspect training program (5 studies, MD = −1.59, [95% CI: −5.15, −0.03]), balance training (3 studies, MD = −1.58, [95% CI: −2.55, −0.62]), and aerobic training (3 studies, MD = −1.65, [95% CI: −2.53, −0.77]). By contrast, vibration (2 studies, MD = −0.56, [95% CI: −2.05, 0.93]) and dual-task training (1 study, MD = 0.24, [95% CI: −6.4, 6.88]) exhibited no significant effects.

Conclusion: Physical therapy, especially multi-aspect physical therapy such as muscle strengthening, coordination training, gait training, and ADL training, may reduce DCA symptoms. Further, balance and aerobic training can be added to the program. However, the estimated effect size may change in future studies because of the serious RoB, very low certainty of evidence, and high heterogeneity with SARA as the primary outcome. High-quality RCTs are

required to establish evidence for the effectiveness of physical therapy in patients with DCA.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=493883, identifier: CRD42024493883.

KEYWORDS

cerebellum, ataxia, degenerative cerebellar ataxia, physical therapy, physical rehabilitation, systematic review, meta-analysis

1 Introduction

Degenerative cerebellar ataxia (DCA) includes various neurodegenerative disorders characterized by progressive cerebellar dysfunction and Purkinje cell loss, leading to cerebellar atrophy (1). Degeneration of the cerebellum, brainstem, or spinal cord can induce diverse clinical symptoms. Limited treatment options improve daily activities and quality of life (QOL), highlighting the need for novel, safe, and effective non-pharmacological interventions (2, 3). Physical therapy (PT) and neurorehabilitation have shown potential as interventions for cerebellar ataxia (4, 5), but the precise effect estimates and the certainty of their effectiveness have not been thoroughly evaluated.

The effects of PT on DCA have been examined in randomized controlled trials (RCTs) and systematic reviews (5). The most recent systematic review included eight articles for meta-analysis, of which six examined the effects of PT on the Scale for Assessment and Rating of Ataxia (SARA) as the primary clinical outcome for DCA (6, 7). However, one was not an RCT and two did not focus on spinocerebellar disease (SCD). Previous studies examining the effects of therapeutic exercise on cerebellar ataxia identified several limitations, including variability in the control groups used. First, the quality of included studies varies widely, which may affect result reliability. Specifically, the quality of evidence regarding functional independence is low, making the conclusions difficult to generalize. Second, studies are focused on non-hereditary degenerative and acquired cerebellar ataxia; data on hereditary cerebellar ataxia remain sparse. Additionally, the sample sizes in these studies are often small, and the treatment durations are short, limiting the ability to evaluate long-term effects. Last, the reported results show inconsistencies and potential for bias, particularly in non-randomized studies.

Another critical limitation of previous studies is the variability in the control groups used. While some studies utilized passive controls (e.g., no intervention), others employed active controls (e.g., alternative physiotherapy methods or standard care). This distinction is particularly important as the use of active control groups is increasingly common due to ethical considerations in rehabilitation trials, where withholding treatment from control participants may be deemed inappropriate (8). However, this trend complicates the interpretation of findings and the synthesis of results in meta-analyses, as the comparator conditions can substantially influence the observed treatment effects. A clearer understanding of the relative effectiveness of interventions under different control conditions is essential for clinical decision-making.

These limitations highlight the need for high-quality, large-scale studies to clarify the benefits of therapeutic exercise in this population. Several RCTs have been conducted since then to address the issues raised in this systematic review. However, a new systematic review updating the effect estimates for PT and showing improved certainty is lacking.

Thus, this systematic review and meta-analysis aimed to investigate the effects of a multi-aspect PT program, including strength training, coordination training, aerobic exercise, balance training, gait training, activity of daily living (ADL) training, and vibration stimulation, on SARA as the primary outcome of ataxia severity. In addition, we included the following secondary outcomes unaddressed in previous systematic reviews: International Cooperative Ataxia Rating Scale (ICARS) (6), Berg Balance Scale (BBS) (9), Balance Evaluation Systems Test (BESTest) (10, 11), functional independence measure (FIM) (12), QOL-related indicators (13), and gait ability. Furthermore, we analyzed the results separately for passive and active control groups to better understand the impact of different comparators on treatment outcomes. The findings of this study are expected to contribute to future research questions and decision making for clinical interventions.

2 Methods

2.1 Overall

This systematic review was conducted in accordance with the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (see Supplementary material "PRISMA checklist") (14). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: 2023 CRD42023379192).

2.2 Eligibility criteria

The inclusion criteria for selecting studies in this review included the following: (1) randomized controlled trials (RCTs), (2) participants with DCA, (3) the use of PT as an intervention, and (4) articles written in English. The exclusion criteria were as follows: (1) studies that were not RCTs and (2) conference papers, protocol papers, or registration reports.

DCA comprises a diverse range of disorders, which include autosomal dominant spinocerebellar ataxia (15), spinocerebellar

ataxia (SCA) (16–18), Friedreich's ataxia (FA) (19), multiple system atrophy with cerebellar involvement (20), and sporadic adult-onset ataxia of indeterminate cause (21). Given this heterogeneity, our systematic review intentionally broadened its scope beyond any single phenotype, such as SCA, to ensure a comprehensive analysis.

2.3 Information sources and search strategy

We searched the PubMed, Cochrane Central Register of Controlled Trials, CINAHL, and PEDro databases for studies published in English and involving human participants. We developed a search query for these databases (Appendix 1). The search was performed on March 8, 2024 and included all articles published up to that date.

2.4 Article selection

The search was conducted by independent reviewers (Akiyoshi Matsugi and Hiroaki Tanaka) using the specified databases, and the initial list of articles was verified by other reviewers. In addition, manual searches were performed with relevant keywords such as "cerebellum," "spinocerebellar degeneration," "ataxia," "physiotherapy," and "rehabilitation." The studies identified in the databases were managed using Rayyan (Cambridge, MA) and ENDNOTE 20 (Clarivate, Philadelphia, PA).

2.5 Data collection

For each study, the two independent reviewers, selected at random from a pool of 11 individuals (Akiyoshi Matsugi, Kyota Bando, Yuki Kondo, Yutaka Kikuchi, Kazuhiro Miyata, Yuichi Hiramatsu, Yuya Yamanaka, Hiroaki Tanaka, Yuta Okuda, Koshiro Haruyama, and Yuichiro Yamasaki), were tasked with screening the titles and abstracts to assess eligibility for inclusion. Full-text assessments were undertaken when deemed necessary. Initially, the reviewers were blinded to each other's identities to mitigate potential biases, and any discrepancies in judgment were adjudicated by a third reviewer. The identities of the reviewers were disclosed during the final deliberation to ensure transparency. Extraction of data, encompassing study design, methodological approach, participant demographics, baseline characteristics, sample sizes, and outcome measures, was independently conducted by the two reviewers. Any inconsistencies in data extraction were resolved through consultation with a third reviewer. In case of missing data, corresponding authors were contacted; if responses were not received or data were not provided, analyses were confined to the available data. Extracted data were systematically organized using a Microsoft Excel spreadsheet.

2.6 Data items

We assessed ataxic symptoms using SARA as the primary outcome (6). The use of this scale is recommended for assessing cerebellar ataxia as a clinician-reported outcome measure (22). The secondary outcomes included ICARS (23), gait speed, dynamic gait index (DGI) (24), FIM (25), Inventory of Non-Ataxia Signs (INAS), Euro Quality of Life Visual Analog Scale (EQ-VAS), BBS, and other reported outcomes that the reviewers considered important. Other additional important outcomes selected by the reviewers included fall frequency, Activities of Balance Confidence questionnaire (ABC), functional ambulatory capacity (FAC) (26), 8-meter walk test (8MWT), timed up and go test (TUG), modified Clinical Test Sensory Interaction and Balance (mCTSIB), 9-hole peg test (9HPT), Barthel index (BI), MOS 36-Item Short-Form Health Survey (SF-36), Euro quality of life 5 dimension (EQ-5D), and Friedreich's Ataxia Rating Scale (FARS).

The weighted mean difference and the mean and standard deviations (SDs) were used for continuous data in the primary and secondary outcomes. The mean difference was used to summarize multiple measures of the same outcome items.

2.7 Study risk of bias assessment

The risk of bias (RoB) was evaluated using the Cochrane RoB tool (version 2.0) (27). Two out of five independent reviewers conducted a critical appraisal of the studies included in the analysis. The assessment focused on the following areas: (1) bias originating from randomization; (2) bias resulting from deviations from the intended interventions; (3) bias due to incomplete outcome data; (4) bias related to the assessment of outcomes; and (5) bias stemming from the selection of reported results. Each study was classified for each domain as having low, some concern, or high RoB. An algorithm-based approach, guided by responses to signaling questions, was employed to judge the RoB for each domain (27). Any disagreements among the reviewers were discussed If a consensus could not be reached, a third reviewer was consulted to resolve the issue.

2.8 Effect measures and synthesis methods

The primary outcome (SARA) and secondary outcomes (ICARS, BBS, INAS, gait speed, DGI, FIM, and EQ-VAS) were obtained as the mean of the pre-post difference (MD) and SD. The effect sizes were the MD and 95% confidence interval (CI) integrated using RevMan 5.4 for all outcomes.

If more than two randomized (or quasi-randomized) controlled trials reported the same outcomes, the weighted mean difference was calculated using RevMan 5.4 software. Random-effects models were used to obtain pooled estimates, and the results were described using forest plots in RevMan 5.4. If the MD and SD were obtained from the original report, we requested the authors for the data via email. Further, if we could not obtain the SD from the authors, missing SD of MD was calculated using the standard error (SE) or 95% CI. If the MD could not be obtained, we declined to integrate the data from that study into the MA.

To examine the effects of PT, we conducted a meta-analysis without separating subgroups. Subsequently, subgroup analysis was

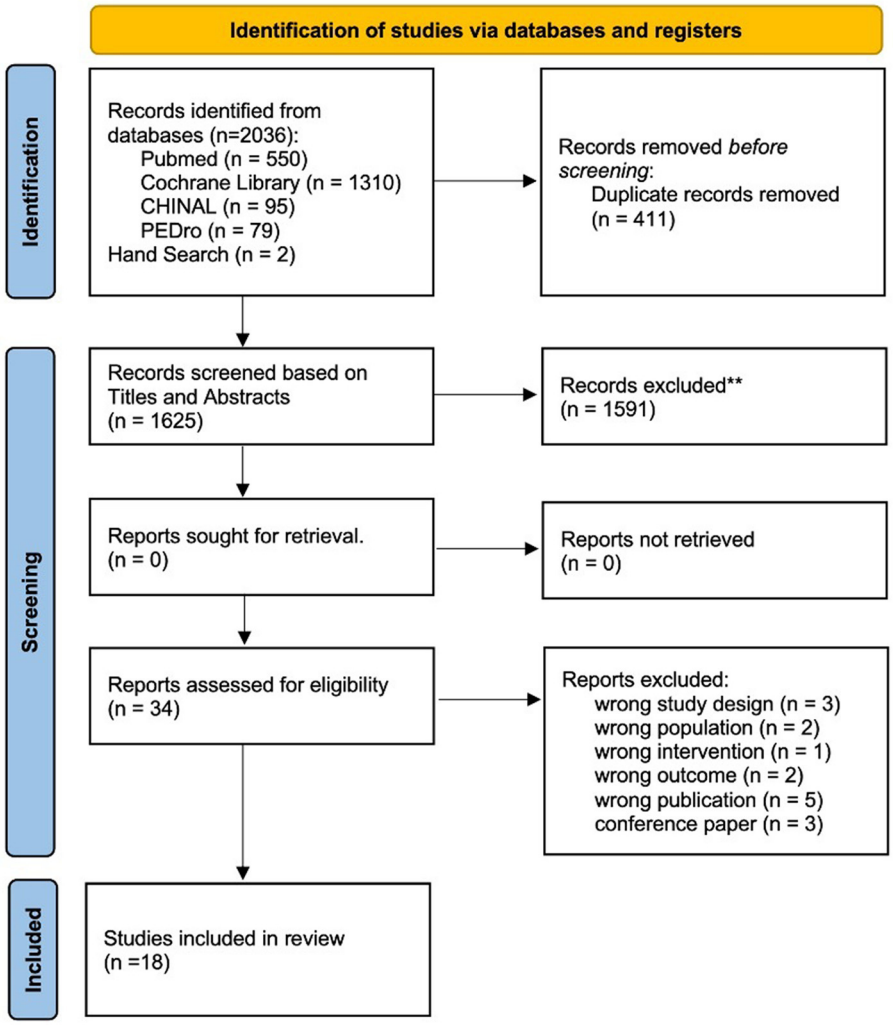

FIGURE 1
Flowchart depicting the article search and selection process according to the PRISMA guidelines. This diagram illustrates the steps taken to identify and screen articles, culminating in the selection of 18 studies that met the inclusion criteria for the systematic review. **Indicates using Rayyan.

performed according to the type of intervention, which was divided into multiaspect PT, balance training, aerobic exercise, vibration, and dual-task physiotherapy.

2.9 Reporting bias assessment

Funnel plots were used to determine publication bias.

2.10 Certainty assessment

The overall quality of the evidence for all outcomes was appraised using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (28) framework. This assessment encompassed several key factors: (1) study design, (2) RoB, (3) inconsistency of results, (4) indirectness of evidence, (5) imprecision of estimates, and (6) additional considerations (28). These elements were utilized to gauge the certainty of the effect estimates, classifying the quality of evidence into one of four categories: "very low," "low," "moderate," and "high" (28).

3 Results

3.1 Study selection

A flowchart of the selection process is shown in Figure 1. The review process was documented using the PRISMA checklist (Appendix 2).

A total of 2,036 articles were retrieved using a database search and additional records. After duplicate elimination, the titles and abstracts of 1,625 publications were selected. Among these, 34 articles underwent full-text screening for eligibility, and 16 articles were excluded based on the following criteria: (1) non-RCT study

TABLE 1 Characteristics of included studies.

No.	References	Study design	Participant	Age and baseline severity	Test of multi or single aspect of physiotherapy intervention	Intervention	Intensity, frequency, duration (for meta-analysis)	Control	Outcome
1	Miyai et al. (4)	RCT	SCA6 ($n = 20$), SCA31 ($n = 6$), Idiopathic DCA ($n = 16$)	Age: Intervention 63.5 ± 11, Control 61.5 ± 11 SARA: Intervention 12.2 ± 3.2, Control 11 ± 3.7	Multi	Intensive Physical Rehabilitation including general conditioning, ROM ex., muscle strengthening, balance tr., walking, stair climbing, OT for improving ADLs.	PT 1 h/day, OT 1 hour/day, 5 day/week, 4 weeks	No intervention	SARA, FIM, Gait speed (m/s), FAC, Falls (per week)
2	Kaut et al. (36)	RCT	SCA1 ($n = 7$), SCA2 ($n = 1$), SCA3 ($n = 11$), SCA6 ($n = 13$)	Age: Intervention 61.2 ± 12.3, Control 57.3 ± 12.7 SARA: Intervention 14.31 ± 5.7, Control 11.63 ± 6.2	Sigle	WBV	5 stimulus trains of 60 s/day, 4 sequent days	Sham-vibration	SARA, 8MW, 9HPT, INAS
3	Seco et al. (40)	RCT	FA ($n = 16$)	Age: Intervention 48.2 ± 3.9, Control 56.4 ± 4.1 100% Wheelchair user No numerical data for ICARS has been reported.	Multi	PT (balance, coordination, weight tr. etc) 60 min/day	5 year, 60 minuets/session, 3 times/week,	No intervention	ICARS, FIM, SF36
4	Chang et al. (34)	RCT	SCA ($n = 20$)	Age: Intervention 48.1 ± 5.47, Control 49.7 ± 7.57 Intervention13.5 ± 9.81 (numerical data in control was not reported)	Sigle	Home-based Cycling regimen	15 min/day, 3 day/week, 4 weeks	No intervention	ICARS
5	Bunn et al. (33)	RCT	SCA6 ($n = 12$)	Age: Intervention 60.2 ± 10.5, Control 58.3 ± 14.5 SARA: Intervention 11.8 ± 6.7, Control 12.3 ± 8.5	Sigle	Home-based balance exercises including balance control engagement under functionally relevant daily scenarios while looking at projected images (optokinetic stimuli)	15 min of training, 5 days per week	No intervention	SARA, FIM, BBS, ABC, EQ-5D, EQ-VAS
6	Milne et al. (37)	RCT	FA ($n = 19$)	Age: Intervention 37.73 ± 9.81, Control 35.94 ± 15.11 FARS: Intervention 101.3 ± 22.49, Control 90.5 ± 21.04	Multi	Outpatient rehabilitation program, including strengthening, postural control, coordination and control, functional mobility, balance training, stretching and mobilizing, and cardiovascular fitness	2–3 h, 3 times/week, 6 weeks	No intervention	BBS, FIM, FARS
7	Wang et al. (43)	RCT	SCA3 ($n = 9$)	Age: Intervention 57[44-61], Control 54[51-60] SARA: Intervention 5[3.5-10], Control 7.5[5.5-13]	Single	Exergames enhancing balance training	40 min/session, 3 sessions/week, 4 weeks	Conventional balance and coordination training (30 min)	SARA, 9HPT [more affectedside], 9HPT [less affectedside]

(Continued)

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TABLE 1 (Continued)

No.	References	Study design	Participant	Age and baseline severity	Test of multi or single aspect of physiotherapy intervention	Intervention	Intensity, frequency, duration (for meta-analysis)	Control	Outcome
8	Rodriguez-Diaz et al. (39)	RCT	SCA ($n = 38$)	Age: Intervention 39.52 ± 10.72, Control 38.78 ± 10.53 SARA: Intervention 15.8 ± 9.7, Control 15.9 ± 9.4 (numerical data was not reported, and estimated from graph)	Multi	Neurorehabilitation therapy, PT: emphasizing on balance, coordination, and muscle strengthening	Total 5.5 h/weekday, (PT 4 h, OT 1 h, psychotherapy 0.5 h), 24 week	No intervention	SARA, INAS
9	Tercero-Perez et al. (41)	RCT	SCA7 ($n = 18$)	Age: Intervention (intensive) 38.6 ± 14.22, Intervention (moderate) 41.33 ± 16.17, Control 39.71 ± 18.17 SARA: Intervention (intensive) 16.4 ± 6.39, Intervention (moderate) 18.58 ± 3.64, Control 15.64 ± 5.33	Multi	Strengthening, coordination tr. Balance tr., Gait tr.	Intensive tr. Group: 2 h/day, 5 day/week, 24 weeks Moderate tr. Group: 2 h/day, 3 day/week, 24 weeks	Non-training	SARA, INAS, Barthel Index
10	Velazquez-Perez et al. (42)	RCT	SCA2 ($n = 14$)	Age: Intervention 38.33 ± 8.23, Control 38.64 ± 10.34 SARA: Intervention 0.87 ± 0.79, Control 0.93 ± 0.85	Multi	Balance, gait, limb coordination training	4 h/day, 5 day/week, 3 weeks	Not receive rehabilitation	SARA, INAS, 9HPT (dominant hand)
11	Barbuto et al. (32)	RCT	SCA ($n = 6$), Idiopathic Ataxia ($n = 7$), MSA-C ($n = 7$)	Age: Intervention 53.8 ± 17.4, Control 46.1 ± 13.3 SARA: Intervention 9.1 ± 2.9, Control 10.35 ± 3.5	Single	Aerobic training with cycling regimen at home	30 min/session, 5 sessions/week, 4 weeks	No training (4 weeks)	SARA, Gait speed (m/s), TUG, DGI
12	Ayvat et al. (29)	RCT, cross-over	SCA ($n = 7$), MS ($n = 13$)	Age: Group1 32 [26–39.5], Control 34 [28–40] (median[IQR]) Numerical ICARS data in baseline of both group were not reported.	Single	Whole body vibration and exercise program	WBV: 4 min/day, Ex.:1 h/session, 3 session/week, 8 weeks	Only exercise program (same time to intervention group)	ICARS, BBS, TUG
13	Barbuto et al. (31)	RCT	DCA ($n = 20$)	Age: 20 to 70 (not reported in each group) SARA: Intervention (Aerobic tr.) 9.1 ± 2.9, Control (Balance tr.) 10.6 ± 3.5	Single	Aerobic training with cycling regimen at home	30 min/session, 5 sessions/week, 4 weeks	Balance training at home (30 min./session, 5 sessions/week, 4 weeks), Contents and difficulty were adjusted by physiotherapist	SARA, Gait speed (m/s), TUG, DGI
14	Ozvar et al. (38)	RCT, Crossover	SCA ($n = 13$), MS ($n = 8$)	Age: 18–50 (not reported in each group) SARA or ICARS were not reported.	Single	WBV	10 min/session, only Single session	local vibration (LV)	Gait speed (m/s)

(Continued)

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TABLE 1 (Continued)

No.	References	Study design	Participant	Age and baseline severity	Test of multi or single aspect of physiotherapy intervention	Intervention	Intensity, frequency, duration (for meta-analysis)	Control	Outcome
15	Jabri et al. (35)	RCT, cross-over	SCA1 ($n = 3$), SCA2 ($n = 3$), FA ($n = 1$), Niemann–Pick C ($n = 2$), ARCA1 ($n = 1$)	Age: Intervention 46 ± 13, Control 48 ± 13 SARA: Intervention 7.17 ± 0.76, Control 5.83 ± 1.61	Single	Home-based coordinative training WITH vibrotactile Sensory Augmentation at home	30 min/session, 5 sessions/week, 6 weeks	Home-based coordinative training WITHOUT vibrotactile Sensory Augmentation	SARA, TUG, mCTSIB, DGI
16	Winser et al. (45)	RCT	SCA1 ($n = 4$), SCA2 ($n = 1$), SCA3 ($n = 9$), SCA6 ($n = 3$), undetected SCA ($n = 2$)	Age: Intervention 48.67 ± 11.3, Control 46.89 ± 12.56 SARA: Intervention 9.58 ± 3.63, Control 10.5 ± 3.99	Single	Tai-Chi as balance tr.	60 min./session, 3 session/week, 12 weeks	Usual care (did not receive Tai-Chi)	BBS, SARA, EQ-VAS
17	Barbuto et al. (30)	RCT	MSA-C ($n = 6$), SCA ($n = 10$), idiopathic DCA ($n = 20$)	Age: Intervention (Aerobic tr.) 54.9 ± 16.4, Control (Balance tr.) 51.1 ± 13.3 SARA: Intervention (Aerobic tr.) 11.7 ± 5.5, Control (Balance tr.) 11.3 ± 3.7	Single	Aerobic training at home	30 min/session, 5 sessions/week, 6 months	Balance training at home	SARA, Gait speed (m/s), TUG, DGI
18	Winser et al. (44)	RCT	SCA1 ($n = 2$), SCA3 ($n = 15$), SCA11 ($n = 2$), Post-infectious cerebellar degeneration ($n = 2$), Unknown cause for ataxia ($n = 11$)	Age: Intervention 50.2 ± 14.41, Control 46 ± 14.05 SARA: no reported numerical value in baseline of both group	Single	Dual-task training (balance training with cognitive task)	60 min/session, 3 session/week, 4 weeks	Single-task training (conventional balance, coordination, and cognition training delivered separately; active control group)	SARA, BBS, EQ-VAS

RCT, randomized control trial; SCA, spinocerebellar ataxia; DCA, degenerative cerebellar ataxia; FA, Friedreich's ataxia; MSA-C, multiple system atrophy-cerebellar subtype; SARA, scale for assessment and rating of ataxia; IQR, interquartile range; PT, physical therapy; OT, occupational therapy; WBV, whole body vibration; INAS, Inventory of Non-Ataxia Signs; 9HPT, 9 hole peg test; TUG, timed up and go test; DGI, dynamic gait index; mCTSTS, modified clinical test sensory interaction and balance; ICARS, International Cooperative Ataxia Rating Scale; BBS, Berg Balance Scale; EQ-VAS, EuroQol visual analog scale.

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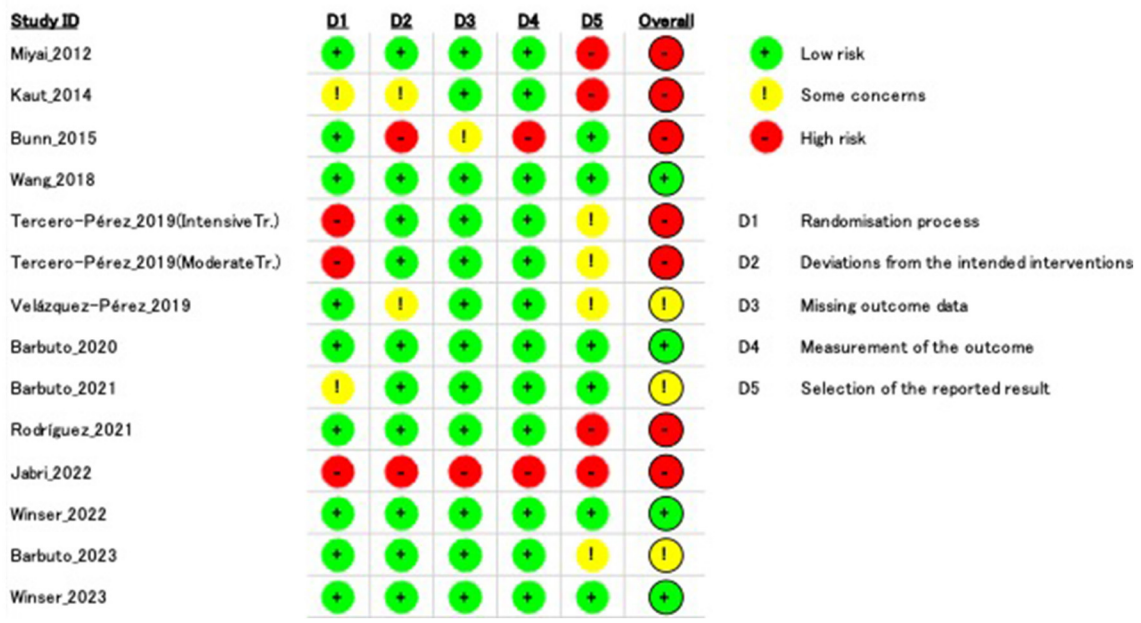

FIGURE 2
Risk of bias (RoB) based on the scale for assessment and rating of ataxia (SARA). "−" indicates "high RoB," "!" indicate "some concerns," and "+" indicates "low RoB."

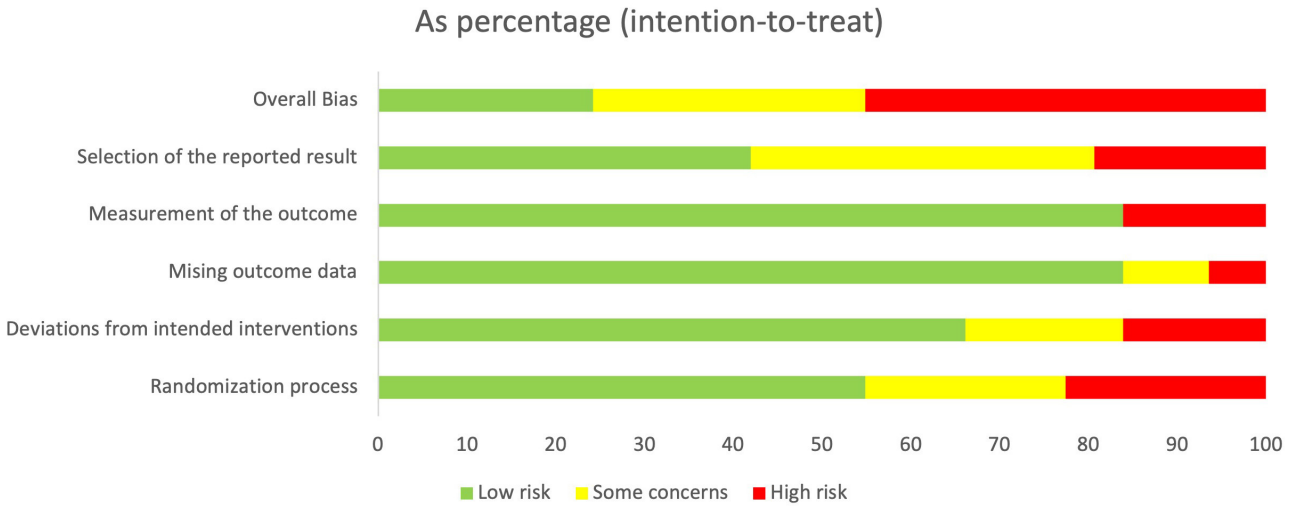

FIGURE 3
Percentage of number of studies about Risk of Bias (RoB) in intention to treat. Horizontal scale indicates percentage of number of studies. Vertical categories indicate the domain of RoB.

design ($n = 3$); (2) non-SCD population ($n = 2$); (3) physiotherapy was not the intervention used ($n = 1$); (4) outcome measure did not include symptoms associated with cerebellar ataxia ($n = 2$); (5) protocol paper ($n = 5$); and (6) conference paper ($n = 3$). Finally, 18 articles (4, 29–45) met the inclusion criteria and were included in the meta-analysis if outcome data were obtained from the publication or authors.

3.2 Study characteristics

The characteristics of the included studies are listed in Table 1. A total of 598 participants were involved in the 18 studies. The most common SCA subtypes were SCA6 ($n = 48$), SCA3 ($n = 35$), SCA2 ($n = 19$), SCA7 ($n = 18$), SCA1 ($n = 16$), and SCA31 ($n = 6$). Thirty-eight patients with FA were included. Many

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cases with unclear pathology were also included. All included studies reported no adverse side effects of physiotherapy. Funding information was insufficient in five studies (29, 36–38, 40). Active control intervention was applied to the control group in seven studies (29–31, 35, 38, 43, 44). Six studies examined the effects of comprehensive interventions that included multiple aspects of PT (4, 37, 39–42).

The following additional outcomes other than the primary or second outcomes were extracted: ABC (46), FAC (47), 8MWT (48), TUG (49), fall frequency, FARS (50), EQ-5D (51), 9HPT (52), modified Clinical Test of Sensory Interaction in Balance (mCTSIB) (53), BI (54), and Short form 36 (55) (Supplementary Figures 8–26).

3.3 RoB in studies

The agreement rate between reviewers for all outcomes across the studies, requiring the support of a third reviewer, was 12.9% (8/62), with full consensus ultimately achieved. Figure 2 and Supplementary Figures 1–7 indicate the RoB for SARA, ICARS, INAS, FIM, DGI, gait speed, BBS, and EQ-VAS. Figure 3 shows the percentages of studies in the six domains and overall bias. In terms of overall RoB, ~40% of the studies were classified as "high risk," and approximately 20% were classified as "low risk."

3.4 Results of syntheses

In case data on the SD_{change} of MD (pre-post) in the original report were insufficient, we requested the data from the corresponding authors. The authors of two studies (34, 36) provided the requested data. We received no responses to our data request for six studies (29, 39–43).

Tables 2, 3 indicate the GRADE quality of the evidence for the primary (Table 1) and secondary (Table 2) outcomes, and the RoBs in these outcomes were "serious" or "very serious."

Individual studies and their effect sizes are shown in Figures 4–9 as forest plots. Overall, physiotherapy had a beneficial effect on SARA (MD = −1.41, 95% CI [−2.16 to −0.66], z = 3.69, p = 0.0002). I^2, a statistic that indicates the level of heterogeneity (56) of the overall effect of PT on SARA, was >80%. Due to the high heterogeneity of the primary outcome, we performed subgroup analyses to explore these factors. We divided the interventions into five subgroups: (1) multi-aspect physiotherapy (MD = −1.59, 95% CI [−3.15 to −0.03], z = 2.0, p = 0.05), (2) balance training (MD = −1.58, 95% CI [−2.55 to −0.62], z = 3.21, p = 0.001), (3) aerobic exercise using cycling regimen (MD = −1.65, 95% CI [−2.53 to −0.77], z = 3.67, p = 0.0002), (4) vibration (MD = −0.56, 95% CI [−2.05 to 0.93], z = 0.73, p = 0.46), and (5) dual-task training (physical training with cognitive task) (MD = 0.24, 95% CI [−6.4 to 6.88], z = 0.07, p = 0.94). No significant difference was observed among the five subgroups (χ^2 = 1.91, df = 4, p = 0.75, I^2 = 0%).

In terms of secondary outcomes, a significant overall effect was observed on ICARS using single-study data (MD = −1.1, 95% CI [−1.77 to −0.43], z = 3.23, p = 0.001) and FIM (MD = 1.39, 95% CI [0.59 to 2.19], z = 3.41, p = 0.0007). In terms of gait speed (m/s),

TABLE 2 Evidence table of SARA as primary outcome.

No. of studies	Certainty assessment						No. of patients		Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physiotherapy	Control	Relative (95% CI)	Absolute (95% CI)		
Scale for assessment and rating of ataxia (scale from: 0 to 40)												
14	Randomized trials	Serious[a]	Very serious[b]	Not serious	Serious[c]	Publication bias strongly suspected[d]	158	157	-	MD **1.41 point lower** (2.16 lower to 0.66 lower)	⊕◯◯◯ Very low	CRITICAL

CI, confidence interval; MD, mean difference; [a]50% of studies were judged as high risk of bias; [b]I^2 > 80%; [c]The sample size was too small (<400); [d] publication bias was estimated by funnel plots. The bold texts indicate important effect size.

TABLE 3 Evidence table of secondary outcomes.

Outcome	Certainty assessment							No. of patients		Effect		Certainty	Importance
	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physiotherapy	Control	Relative (95% CI)	Absolute (95% CI)		
ICARS	3	Randomized trials	Very serious[o]	Serious[e]	Not serious	Extremely serious[c,e]	None	10	10	-	MD **1.1 point lower** (1.77 lower to 0.43 lower)	⊕◯◯◯ Very low	IMPORTANT
INAS	-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
FIM	3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	Publication bias strongly suspected[d]	36	36	-	MD **1.39 point higher** (0.59 higher to 2.19 higher)	⊕◯◯◯ Very low	IMPORTANT
DGI	4	Randomized trials	Very serious[f]	Serious[g,h]	Not serious	Extremely serious[c,i]	Publication bias strongly suspected[d]	40	37	-	MD **0.07 point higher** (1.67 lower to 1.81 higher)	⊕◯◯◯ Very low	IMPORTANT
Gait speed	6	Randomized trials	Very serious[j]	Serious[b]	Serious[k]	Serious[c,i]	Publication bias strongly suspected[d]	84	80	-	MD **0.04 m/s higher** (0.03 lower to 0.11 higher)	⊕◯◯◯ Very low	IMPORTANT
BBS	4	Randomized trials	Serious[a]	Very serious[l,m]	Not serious	Very serious[m]	None	25	26	-	MD **3.95 point higher** (1.94 lower to 9.84 higher)	⊕◯◯◯ Very low	IMPORTANT
EQ-VAS	3	Randomized trials	Serious[n]	Not serious	Not serious	Serious[c]	None	30	32	-	MD **6.84 % lower** (14.44 lower to 0.76 higher)	⊕⊕◯◯ Low	IMPORTANT

CI, confidence interval; MD, mean difference; [a]50% of studies were judged as high risk of bias, [b]$I^2 > 80\%$; [c]The sample size was too small (<400); [d]publication bias was estimated by funnel plots; [e]Single publication; [f]25% of study was judged as High risk of bias, and 75% of studies were judged as Some concerns; [g]effect direction was inconsistent; [h]$I^2 > 90\%$; [i]divergence in 95% CI; [j]4/6 were Some concerns and 1/6 study was High RoB; [k]one publication (39) included participant with MS; [l]$I^2 > 40\%$; [m]The MD and SD were not reported in 2 studies (30, 34); [n]1/3 study was judged as High RoB; [o]2/3 studies were judged as High RoB. The bold texts indicate important effect size.

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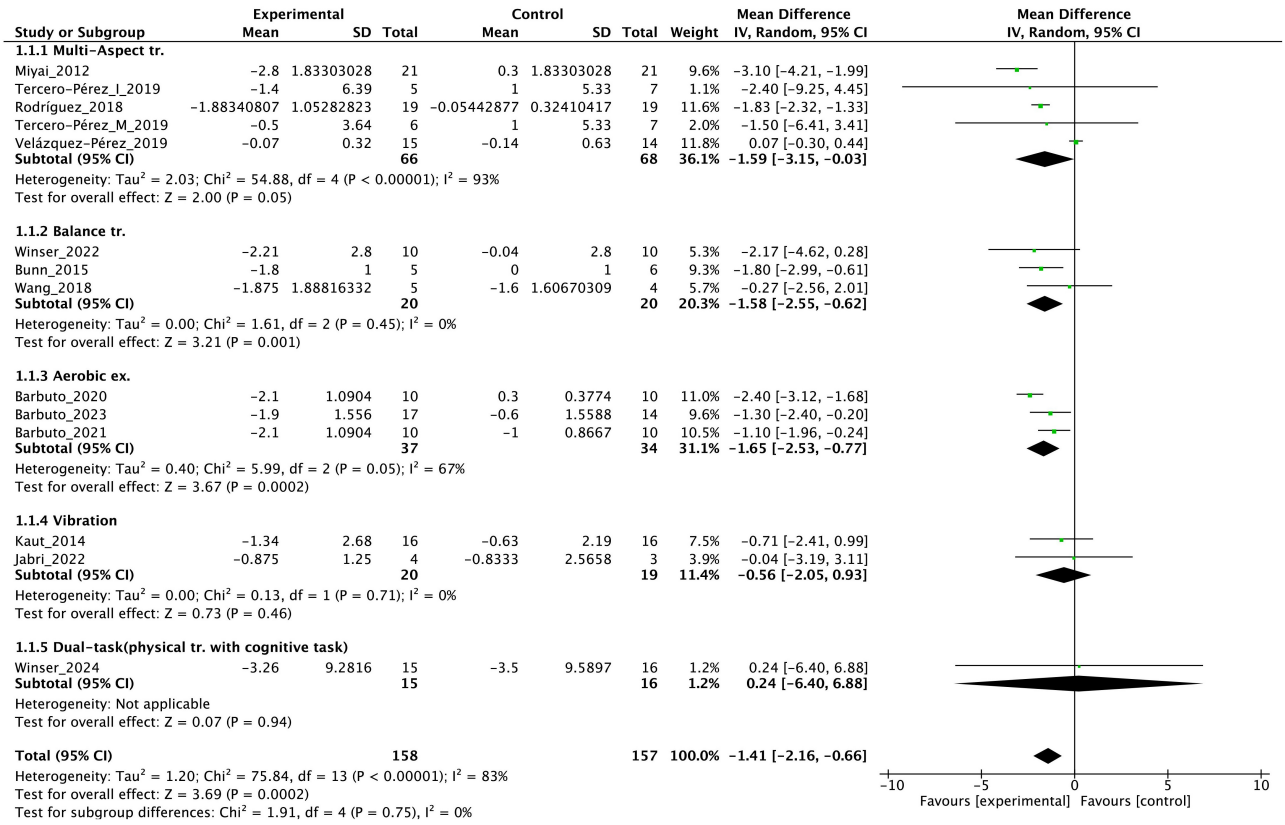

FIGURE 4
Forest plot analysis based on the scale for the assessment and rating of ataxia (SARA) as primary outcome.

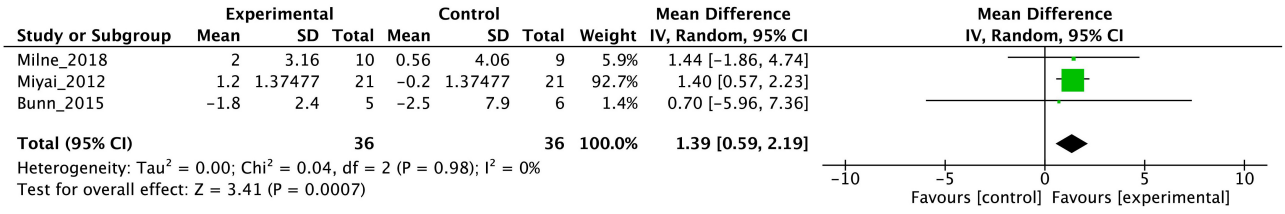

FIGURE 5
Forest plot analysis based on the functional independence measure (FIM) as one of the secondary outcomes.

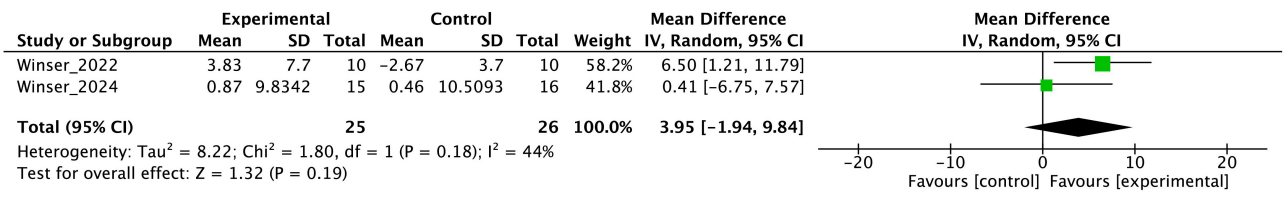

FIGURE 6
Forest plot analysis based on the Berg balance scale (BBS) as one of the secondary outcomes.

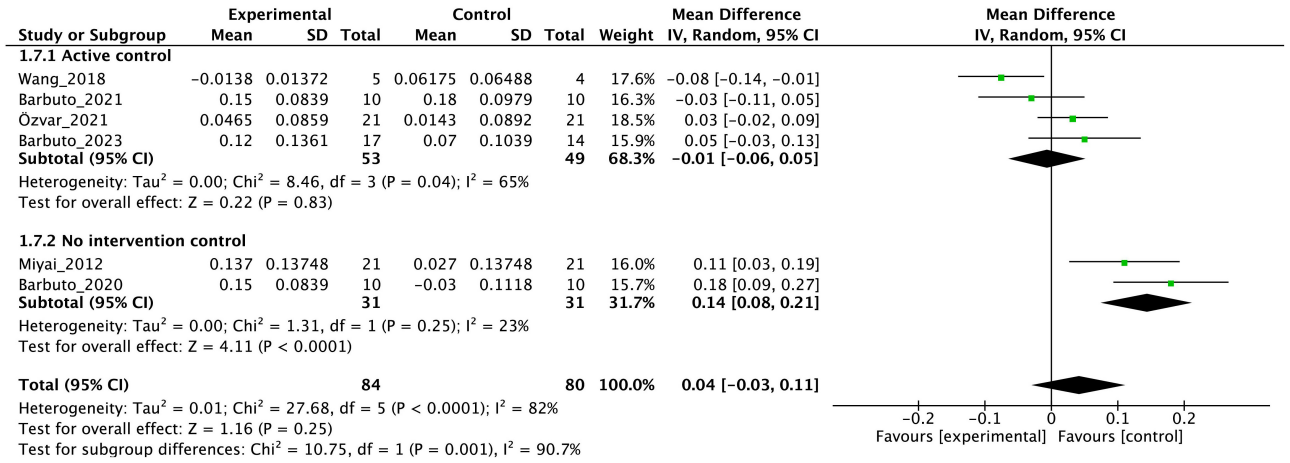

FIGURE 7
Forest plot analysis based on gait speed as one of the secondary outcomes.

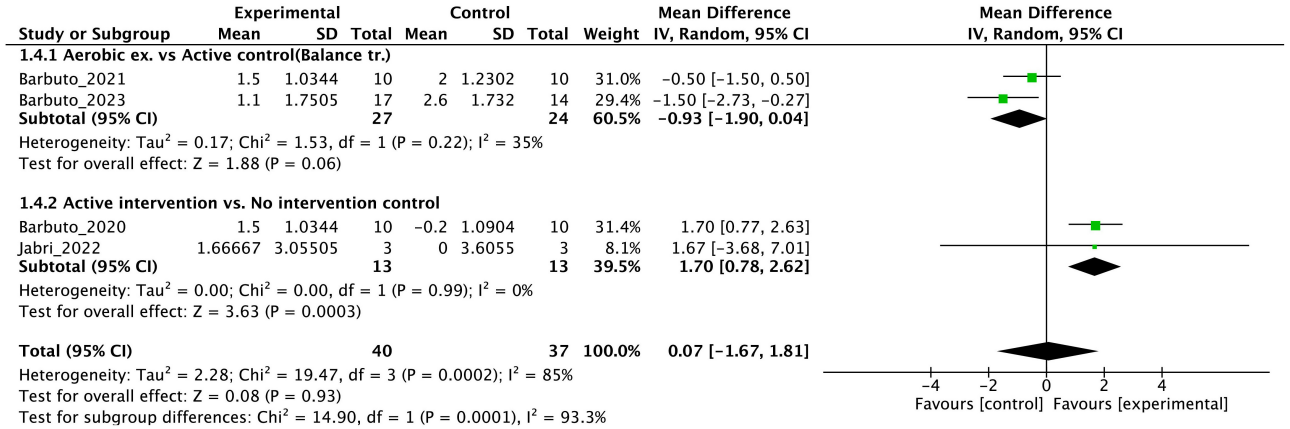

FIGURE 8
Forest plot analysis based on the Dynamic gait index (DGI) as one of the secondary outcomes.

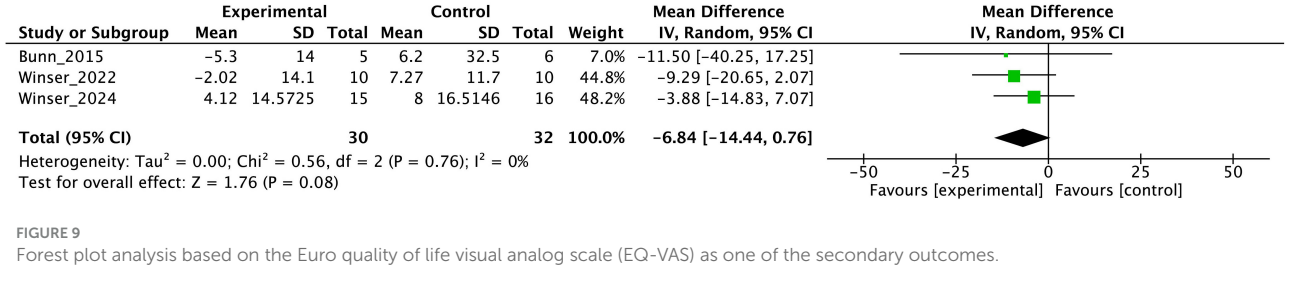

FIGURE 9
Forest plot analysis based on the Euro quality of life visual analog scale (EQ-VAS) as one of the secondary outcomes.

overall effect was not significant (MD = 0.04, 95% CI [−0.03 to 0.11], z = 1.16, $p = 0.25$, $I^2 = 82\%$). Subgroup analysis suggested a significant effect in the no-intervention control group setting (MD = 0.14, 95% CI [0.08 to 0.21], z = 4.11, $p < 0.0001$) but not in the active control group setting (MD = −0.01, 95% CI [−0.06 to 0.05], z = 0.22, $p = 0.83$).

3.5 Reporting biases

Publication bias was suspected based on funnel plots for SARA all over the result (Figure 10). However, when judging each subgroup, the number of reports for each is <10, so it is difficult to fully estimate publication bias.

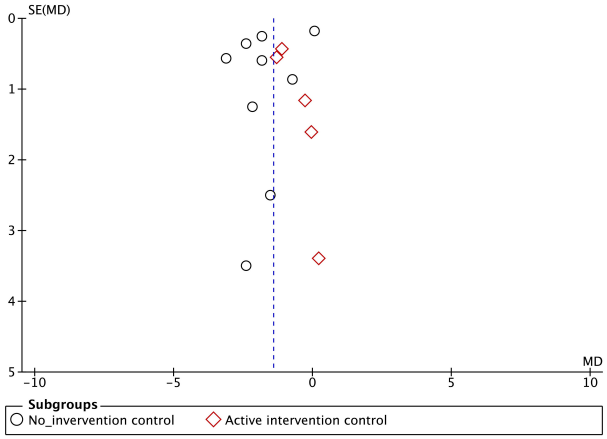

FIGURE 10
Funnel plot of the scale for assessment and rating of ataxia (SARA). SE, standard error; MD, mean difference.

The funnel plot for SARA all over the result shows an asymmetrical distribution, with fewer data points in the lower left and lower right regions (Figure 10). This pattern suggests a potential risk of publication bias, as smaller studies with non-significant or unfavorable results may be underreported or unpublished. This asymmetry may influence the overall interpretation of the results, particularly when combined with the limitations of subgroup analyses the number of reports for each is <10. As a result, while the evidence synthesis incorporates these findings, the certainty of evidence should be interpreted with caution.

3.6 Certainty of evidence

The GRADE quality of the evidence of primary outcome SARA was judged as "very low" (Table 2). The RoB was "serious," inconsistency was "very serious" with I^2 >80%, imprecision was "serious" owing to the small sample size ($n < 400$), and publication bias was strongly suspected as the reason for the obvious asymmetry of the funnel plot (Figure 10).

In the secondary outcomes, the result of GRADE quality is shown in Table 3. Notably, INAS data were not obtained from all authors reported in the original publication of INAS. Therefore, none of the results of GRADE were generated. In other secondary outcomes, certainty of evidence was judged as "very low" in ICARS, FIM, gait speed, DGI, and BBS and "low" in EQ-VAS.

4 Discussion

This study evaluated the effectiveness of physiotherapy interventions in patients with DCA. The results of this systematic review and meta-analysis demonstrated that physiotherapy significantly reduces ataxia symptoms with no adverse event, as evidenced by a notable decrease in the SARA scores. Specifically, a multi-faceted physiotherapy approach—including balance, aerobic, muscle strength, coordination, gait, and ADL training—was particularly effective in alleviating ataxia symptoms. These findings support the importance of physiotherapy in patients with DCA and suggest that such approaches may be widely adopted in future clinical practice without severe adverse events. However, this evidence should be used with caution because of various remaining concerns.

First, a high level of statistical heterogeneity (I^2 > 80%) was observed for the primary outcome SARA scores. This heterogeneity could primarily be attributed to the broad range of interventions used. The included studies employed various designs, including multi-faceted interventions, such as muscle strength training, coordination training, gait training, and ADL training, or focused on specific types of training, such as aerobic exercise, balance training, and vibration stimulation. Each of these interventions possibly affected patients through different mechanisms, which potentially led to variability in treatment effects. Additionally, some studies used an active control group rather than a no-intervention control group. This inclusion of active controls possibly introduced effects from non-specific factors, such as placebo or learning effects, contributing to the variability in outcomes. Furthermore, the variation in intervention duration among studies possibly played a role in increasing heterogeneity. Some studies implemented interventions over a few weeks, whereas others extended over several months, which could impact the outcomes differently. Another possible factor is severity of disease and symptoms, and As highlighted by Reetz et al. (57), SARA items related to trunk and lower limb functions may exhibit ceiling effects after the loss of walking ability, reducing their sensitivity to detect disease progression. This limitation could have influenced the observed variability in treatment effects in our analysis, particularly in non-ambulatory patients. Finaly, the effects may differ depending on the type of disease (58, 59), and this may have affected the results. These factors combined contributed to the high statistical heterogeneity observed, making the aggregated results difficult to generalize. When interpreting the findings of this study, we should consider these sources of heterogeneity, carefully evaluating the specific characteristics of each intervention, the type of control groups used, and the influence of intervention duration on the outcomes.

Different from previous systematic reviews (5, 60, 61), the present systematic review and meta-analysis highlighted that aerobic exercise (30–32), such as cycling regimens, can notably reduce cerebellar ataxia symptoms, as reflected in the significant improvements in SARA scores. These exercises contribute to cardiovascular fitness, which may enhance overall endurance and mobility in patients with DCA. The repetitive and rhythmic nature of aerobic activities could also promote neuroplasticity, aiding in the reorganization and adaptation of motor function (34). These findings suggest that incorporating aerobic exercise into rehabilitation programs for people with DCA could support motor aspects of health and thus contribute to a comprehensive therapeutic strategy.

Previous systematic reviews of interventions using non-invasive brain stimulation (NIBS) have shown improvements in SARA scores of over 2.5 points (62, 63), which is greater than the 1.4 points achieved through PT in this study. It is also considerably

lower than SARA's minimally detectable change of 3.5 (64). While PT is a safer intervention suggested by this systematic review, this discrepancy highlights the need to explore the potential benefits of combining PT with NIBS to achieve greater therapeutic effects. A previous study examined the effects of combining repetitive transcranial magnetic stimulation (rTMS) and PT, providing a direction for future research (65), which was not included out SR because this rTMS+PT report was published after our article search for this systematic review. Additionally, whether PT offers advantages over NIBS in maintaining long-term effects should be investigated. These considerations suggest that future strategies for managing symptoms in patients with DCA should focus on integrating PT with NIBS and optimizing PT to sustain its benefits over longer periods, ultimately aiming to enhance the overall QOL for individuals with DCA.

One of the strengths of this study is its broad inclusion of a wide range of outcomes, which provides a comprehensive overview of the effects of physiotherapy on patients with DCA (5, 60, 61). However, the diversity in gait-related indicators, such as different measures of gait speed and balance, poses a challenge for integration and comparison across studies. This lack of uniformity complicates the selection of the most appropriate measures for clinical use (66). Moreover, while patient-reported outcomes (67) are increasingly recognized as important in the rehabilitation of DCA, few studies have utilized QOL-related indicators, highlighting a critical gap in current research. Addressing this gap by incorporating more QOL measures will provide a better understanding of how physiotherapy interventions impact the overall wellbeing and daily life of patients, ensuring that treatment approaches are aligned with patient-centered goals.

The results of this meta-analysis showed the limited effects of PT on secondary outcomes. The significant effects on ICARS and FIM were find, but the numbers of studies and participants were small. In gait ability estimated by gait speed and DGI, subgroup analysis showed an effect in the no-intervention control group but not in the study with active control. These findings reflect the minimal or limited effects of PT on gait. In balance ability, we cannot find significant effect on BBS, indicating the effect of PT on balance ability may be limited with note the studies select active control [usual care (45) or physiotherapy (44)]. In QOL, there was no significant effect on EQ-5D. In non-motor symptoms, we could not obtain INAS data from either study. In secondary outcomes, many studies have adopted active control, and subgroup analysis clearly shows that this has brought down the overall effect size. Therefore, it is necessary to use this evidence about secondary outcome with the understanding that it may be underestimated. Further, RoB were serious or very serious, and certainty of evidence were "low" or "very low". Therefore, in secondary outcome, we cannot enough discuss the effectiveness or certainty of the study at all.

This study has several limitations that are common in systematic reviews and meta-analyses. One of the primary concerns was the high RoB in many of the included studies. The variation in study quality, with some studies having methodological weaknesses, affected the reliability of the overall findings. Furthermore, the certainty of the evidence was judged to be very low, raising concerns about the robustness of the conclusions drawn from this analysis. The publication bias estimated by funnel plot including 13 individual RCTs was judged as high, but the subgroup analysis involved less than 10 RCTs, so as a result, while the evidence synthesis incorporates these findings, the certainty of evidence should be interpreted with caution. These factors indicated that the results of this meta-analysis should not be directly and uniformly applied to clinical practice. Instead, clinicians must carefully consider the context of each patient's condition, the specific nature of the physiotherapy interventions, and the quality of the evidence when integrating these findings into treatment plans. Caution and clinical judgment are essential to ensure that interventions are appropriate and beneficial for individual patients with DCA.

Another notable limitation of this study was the small number of studies and the low certainty of evidence for the seven secondary outcomes selected: ICARS, FIM, gait speed, DGI, BBS, EQ-VAS, and INAS. The limited data available on these outcomes and the variability in reporting restricted the ability to draw firm conclusions about their efficacy. Thus, a core outcome set that standardizes the measurement and reporting of critical outcomes must be established in clinical trials involving patients with DCA. Establishing such a core set would enhance comparability across studies, improve the reliability of evidence synthesis, and ensure that all clinically relevant aspects of DCA are comprehensively evaluated, ultimately leading to better-targeted and more effective rehabilitation interventions.

Research into physiotherapy for DCA faces several challenges primarily because of the heterogeneity of the disease. DCA encompasses various subtypes, each with distinct pathologies and clinical presentations, leading to a wide range of symptoms and rates of progression among patients (1). This diversity complicates the design of standardized therapeutic interventions and hinders the ability to generalize findings across different DCA subtypes (68). Moreover, as a rare disease, DCA presents difficulties in recruiting sufficient sample sizes for robust clinical trials (69), which impacts the statistical power and reliability of the studies. In addition to ataxia, patients with DCA may experience cognitive impairments, spasticity, and general physical decline, which vary between individuals (70). These peripheral symptoms further complicate the assessment of physiotherapy outcomes. Thus, interventions may need to be tailored to address not only the primary ataxia symptoms but also these associated conditions. Addressing these issues requires comprehensive and adaptable research approaches that consider the full spectrum of DCA symptoms and their impact on patient health and QOL.

Another limitation of this study was that the integrated effects were based solely on data collected immediately after the intervention. The study did not account for the varying lengths of the intervention periods, which ranged from as short as 4 weeks to as long as 6 months, and even up to 5 years in some cases. Furthermore, this analysis did not investigate the duration for which the intervention effects are sustained over time. Interventions showing no immediate effect are unlikely to yield significant benefits 6 months post-intervention. However, for those interventions that demonstrated immediate positive effects, further research is needed to explore the long-term sustainability of these benefits. Future studies should focus on examining the persistence

of the therapeutic effects of physiotherapy over extended periods to clarify the long-term impact of this intervention in patients with DCA.

In the context of clinical rehabilitation for progressive neurodegenerative diseases, it is essential to consider the selection of appropriate programs, the number and frequency of sessions, the optimal timing for initiation, and the customization of interventions based on the disease stage. However, this systematic review does not provide definitive answers to these questions due to the limitations of the available evidence. Given the potential benefits of physiotherapy from the early stages of the disease (42), as well as its efficacy even in cases where walking becomes difficult (40), we believe it is crucial to initiate and maintain physiotherapy as early and consistently as possible. Additionally, since the effects of physiotherapy can be sustained but may diminish over time (4), long-term intervention programs that are easy to implement and safe for home use are essential (30–32, 34). Tailoring rehabilitation programs in multiaspect with flexible intensity to address each patient's specific symptoms is a key responsibility of physiotherapists (4, 39, 41, 42), as individualized care can optimize outcomes. To provide clearer answers to these critical questions, further high-quality RCTs are urgently needed.

As mentioned above, there are many problems with physical therapy research on DCA. Nevertheless, the results of this research provide information on the factors necessary for obtaining an effect. Multi-aspect PT programs, incorporating approaches such as muscle strengthening, balance training, coordination exercises, and aerobic training, have demonstrated significant benefits for mitigating ataxia symptoms and improving overall QOL in patients with DCA. These comprehensive programs address the complex needs of patients by targeting multiple dimensions of motor function simultaneously. However, the intensity of these interventions, often exceeding 2 h per day, 5 days a week, necessitates careful planning to align with each patient's capacity and endurance, ensuring feasibility and sustainability. Tailored therapy regimens are essential to optimize outcomes while accommodating individual health conditions.

In conclusion, this systematic review and meta-analysis indicate that physiotherapy, particularly a multi-aspect approach, can significantly reduce ataxia symptoms in patients with DCA. While the findings support the incorporation of various PT interventions into patient care, the overall low certainty of evidence and high RoB necessitate careful consideration when applying these results in clinical settings. Further high-quality research is needed to strengthen the evidence base and provide clearer guidance on the most effective physiotherapy strategies for managing DCA. Nevertheless, the demonstrated safety and potential benefits of these interventions offer promising directions for improving the management and QOL of individuals with DCA.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. KB: Data curation, Writing – review & editing. YKo: Data curation, Writing – review & editing. YKi: Data curation, Supervision, Writing – review & editing. KM: Data curation, Supervision, Writing – review & editing. YH: Data curation, Writing – review & editing. YYaman: Data curation, Writing – review & editing. HT: Data curation, Validation, Writing – review & editing. YO: Data curation, Writing – review & editing. KH: Data curation, Writing – review & editing. YYamas: Data curation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Study protocol for a nested process evaluation of a complex discharge planning intervention (HOME Rehab) to improve participation after first-stroke

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Introduction: Stroke is a leading cause of adult disability, and the transition from hospital to home can be fraught with challenges. The HOME Rehab trial is designed to address if better health outcomes for stroke survivors can be achieved with a contextually relevant and tailored occupational therapy discharge planning and support intervention. Process evaluations inform clinical trial findings and future scale up, as well as how to implement a successful intervention effectively into policy and practice. This paper describes the protocol we are using in the HOME Rehab process evaluation planning and activities.

Methods: Using a theoretically informed approach, mixed methods are being used to collect data and address all aspects of the RE-AIM framework. Quantitative data will comprise clinician surveys, trial logs and fidelity checklists as well as screening and recruitment numbers. Semi-structured interviews with trial participants and carers and focus groups with occupational therapists will provide qualitative data. A concurrent triangulation approach will be taken to draw on the strengths of multiple methods to cross-validate findings. The RE-AIM framework will be used to interpret the qualitative and quantitative data together as well as highlight areas of convergence or divergence in the findings. Multiple data sources will be integrated to refine the interpretation of outcomes, understand the context of program delivery, and identify key findings. Drawing on, and integrating data from, multiple perspectives and methods will strengthen the overall findings and provided detailed insights into the causal mechanisms as well as the contextual factors that may influence intervention outcomes.

Discussion: Process evaluations can optimize study outcomes by improving how a complex intervention is implemented, informing the actions of policymakers and clinicians. For the HOME Rehab intervention, the process evaluation may provide valuable data necessary to explain the trial findings, as well as inform future scale-up and implementation if the HOME Rehab intervention is shown to be effective.

Clinical trial registration: https://www.anzctr.org.au, identifier ACTRN12618001360202.

KEYWORDS

stroke rehabilitation, discharge planning, rehabilitation, occupational therapy, clinical trials, qualitative

1 Introduction

Globally, stroke is the leading cause of disability in adults and each year millions of stroke survivors must adapt to a life with restrictions in activities of daily living as a consequence (1). Stroke rehabilitation interventions, tested first in clinical trials and then translated into practice, reduce disability after stroke (2). Conducting process evaluations alongside clinical trials, and embedding theoretical frameworks within process evaluations, ensures trials effectively inform stroke policy and practice (3–5), providing vital evidence about how an intervention does or does not work, how an intervention is implemented, its mechanisms of impact, and the contextual factors that impact on the intervention. All of which provides details for scale up and replication in different settings should the program be effective (5).

The United Kingdom Medical Research Council (MRC) recommends that researchers conduct process evaluations alongside clinical trials (6). When implementing complex intervention, such as the HOME Rehab trial (7), process evaluations are particularly useful for understanding multiple interacting components, variable outcomes, and the new behaviors required by the people delivering or receiving the intervention (8). Key domains recommended to be evaluated in a process evaluation within the MRC guidance (context, quality of implementation and mechanisms of the intervention) are often augmented in process evaluations from established evaluation frameworks such as the Reach, Effectiveness, Adoption, Implementation and Maintenance framework (RE-AIM) (9). Together, these guidelines and frameworks seek to enable research translation from clinical trials to clinical practice.

1.1 About the HOME Rehab trial

The HOME Rehab trial is designed to address if better health outcomes for stroke survivors can be achieved with a contextually relevant and tailored occupational therapy discharge planning and support intervention; the full clinical trial protocol and intervention components has been published elsewhere (7). The HOME Rehab intervention was developed to address the known challenges experienced when transitioning from hospital to home after stroke, with some returning to hospital soon after discharge (10–12). Compared with transitions to nursing homes, transitions to home after stroke are associated with increased risk of readmission or emergency department visits (13), suggesting there are factors in the home environment which likely contribute to a patient's early readmission. This context is perhaps complicated by the known insufficient communication and service coordination during discharge planning (14–16) with stroke survivors reporting they struggle with independence, social participation and resuming usual activities (17–20). With the numerous contextual factors and the complexity of the HOME Rehab trial (multiple sites, multiple states and health jurisdictions; interacting intervention components; collection of primary and secondary outcomes), conducting a process evaluation nested within the HOME Rehab trial will provide key evaluation data that will support interpretation of effectiveness data. This process evaluation will provide insights into how the intervention either worked or did not, explaining differences in outcome, and gain insights into the experience of both trial participants as well as clinicians working in rehabilitation.

1.2 Objective of the process evaluation

The overall aim of the process evaluation is therefore to explain the trial findings, as well as inform future scale-up and implementation if the HOME Rehab intervention is shown to be effective. If effective, understandings about implementation of the intervention, its mechanisms of impact, and contextual factors influencing delivery and functioning of the intervention will critically inform evidence-based stroke policy and practice (5).

Therefore, the specific objectives of the HOME Rehab Trial process evaluation are to:

- describe the characteristics of participating hospitals and participants to assess reach;
- explore the effects of individual intervention components on the primary outcome of participation;
- describe the perceived effectiveness of relevant intervention components [including the relationship between the participant and their occupational therapist, the importance of goals set, the in-hospital component (including the pre-discharge visit to the home), the community component (including the General Practitioner (GP) liaison), and staff training] from the participant, carer and occupational therapist perspectives;
- describe the perceived acceptance of the HOME rehabilitation intervention by involved occupational therapists and how their attitudes may or may not have shifted after training and involvement in the trial;
- outline the HOME Rehabilitation experimental intervention as delivered in terms of quality, quantity, adaptations and variations (planned and unplanned); and
- estimate the extent to which intervention delivery is normalized among the intervention healthcare professionals and related practice staff at the completion of the trial.

2 Methods and analysis

2.1 Design

The HOME Rehab trial is a multicenter, phase III RCT being conducted in Australia with concealed allocation, blinded measurement and intention-to-treat analysis (7). The setting is in-hospital rehabilitation centers across the states of New South Wales, Queensland, South Australia and Victoria; a list of trial sites is available on the trial registry. The MRC guidelines for process evaluation will provide an overall conceptual framework to evaluate the HOME Rehab trial (5), collating data on context (how context affects implementation and outcomes), implementation (what is implemented and outcomes) and mechanisms

of the intervention (how the intervention produces change). These guidelines also emphasize the need to clarify the key causal assumptions made in developing the HOME Rehab intervention, which are outlined in Figure 1. Figure 1 shows these causal assumptions made, how they inform the key functions of the process evaluation, and how this will contribute to interpretation of outcomes from the main trial.

Within this mixed method process evaluation, the RE-AIM framework (9) will be applied to understand and describe the reach, effectiveness, adoption, implementation and maintenance of the HOME Rehab intervention. These five domains of the REAIM framework will enable a comprehensive, mixed-methods evaluation, one which will systematically explore implementation of the HOME Rehab intervention in the trial and allow the research team to prepare for 'real world' implementation as outlined in the logic model for the process evaluation (Figure 2).

2.2 Process evaluation study population

The process evaluation has been integrated into the randomised controlled trial (RCT) design of the HOME Rehab trial, and will therefore involve stroke clinicians (occupational therapists) working at participating centers, stroke survivors aged ≥45 years (HOME Rehab Trial participants), carers (of HOME Rehab Trial participants) and HOME Rehab trial occupational therapists.

2.3 Process evaluation methods

A mix of quantitative and qualitative approaches will therefore be used to address the aims of process evaluation (Table 1). A concurrent triangulation approach will be taken to draw on the strengths of multiple methods to cross-validate findings (21).

To address the 'reach' REAIM dimension, the HOME process evaluation will collect data on the characteristics of participating hospitals and participants. The representativeness of participating hospitals and participants will be evaluated against Australian stroke statistics including hospital length of stay and bed numbers; participant age, and stroke severity. Further, we will maintain an audit of trial recruitment log to record the willingness of potential participants to participate in the study. This will provide information on the proportion of eligible/invited potential participants who enrol in trial. Reasons for potential participant's non-participation will be included from each site's log.

For the effectiveness dimension, the process evaluation will explore perceptions of the benefits of individual intervention components on the primary outcome of participation. Each intervention component has been outlined in the published protocol (7), allowing the interviewer to qualitatively explore perceived effectiveness of, for example, the pre-discharge visit separately to the goal setting component. To triangulate data and gain detailed understandings, semi-structured interviews with participants and carers, and focus groups with occupational therapists will explore the mechanisms through which the intervention brings change. Knowledge about the mechanism is vital for understanding how and why the intervention is or is not effective and for future replication.

To explore patient and carer perspectives, the trial coordinator will prepare a list of participants from the HOME Rehab trial who have completed their 4-week assessment but are within 12 months of discharge (noting demographics and attributes to facilitate maximum variation sampling). Potential process evaluation participants and carers will then be contacted by phone and invited to participate in a

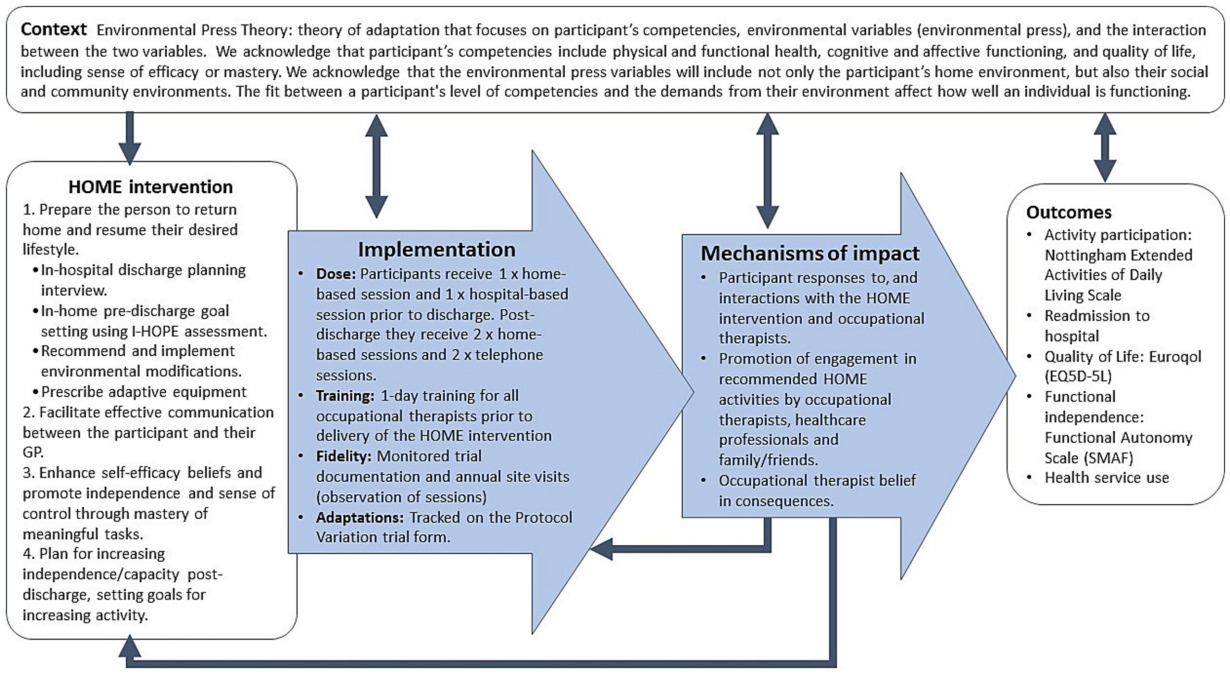

FIGURE 1
Key functions of the HOME trial process evaluation and relationships amongst them. Blue boxes represent components of process evaluation, which are informed by the causal assumptions of the HOME Rehab experimental intervention, and inform the interpretation of outcomes from the main trial.

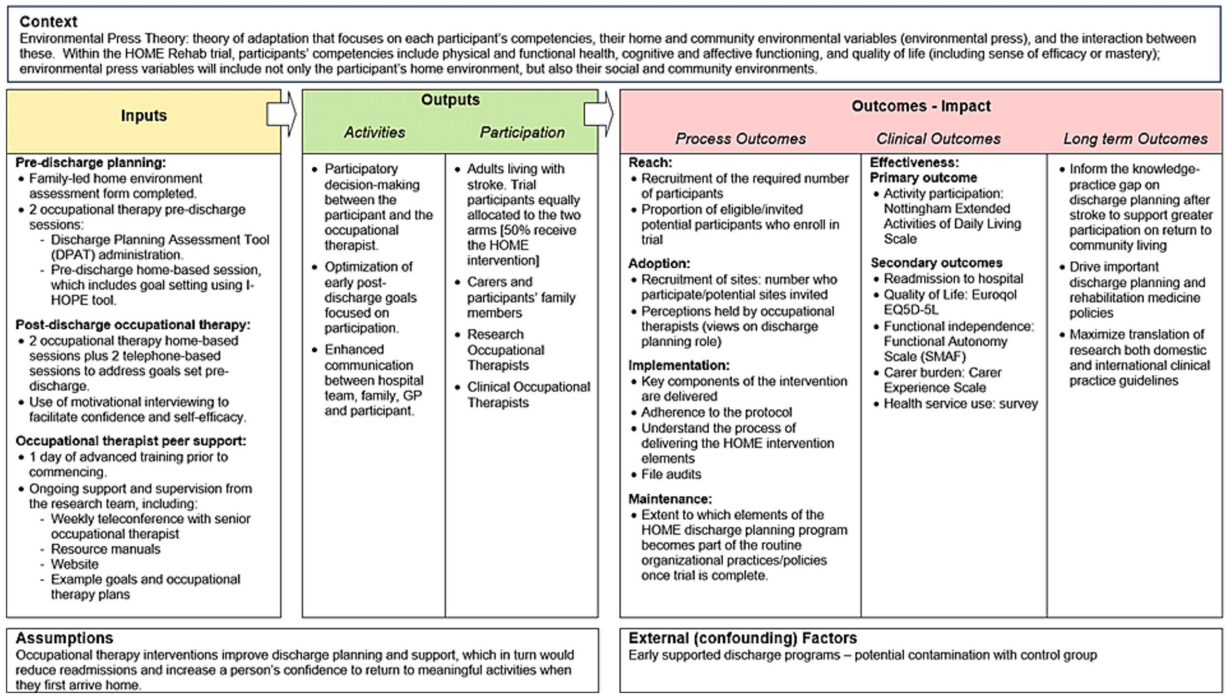

FIGURE 2
Logic model of the HOME trial process evaluation.

telephone interview. To ensure a range of participants are recruited, variation in sampling will be based on gender, severity of impairment, residential status (living alone/ not alone), study group (control/ experimental), and trial site. Patients and carers who agree to an interview will be telephone interviewed by an occupational therapist trained in qualitative interviewing and not involved in delivering trial interventions. At the commencement of the interview, verbal consent to participate with will be audio recorded along with the rest of the interview and sent for professional transcription. Stroke survivor participants and carer interviews will be conducted separately to enable each participant to speak freely about their experience of discharge from rehabilitation and engagement in the trial. The semi-structured interview guide is based on the aims of the trial, process evaluation, and previous process evaluations. The guide was pilot tested and minor changes to the order of questions were made. Semi-structured interviews with approximately 14–16 people with stroke and 10–12 carers from both the experimental and control groups will explore perceptions of discharge planning, transition to home, adherence to self-monitoring, and social support. Additionally, the relationship between the participant and their occupational therapist, perceptions of goal setting and pre and post discharge visits (tailored to study group), sessions with GP involvement (intervention group only) and suggestions for improvement will be explored.

To explore the perspective of trial occupational therapists, focus groups will be held at selected trial sites. Recruitment will aim to obtain data from a sample across the sites with maximum variation in terms of gender, experience, and involvement in the trial. There will be four focus groups with 6–8 therapists in each group and facilitated by an independent researcher. In the focus groups, occupational therapists working within the trial will explore their experiences with discharge planning and the process of delivering the HOME intervention including training, being involved in the trial, implementing the intervention, and the aspects of the trial went well or not so well. Further, adherence to the protocol including implementation barriers and enablers encountered and suggestions for improvement will be explored. Insights gained will provide detailed information to understand the mechanisms of impact of the intervention on the trial outcomes.

To explore 'adoption' the process evaluation will describe the perceived acceptance of the HOME intervention by involved occupational therapists and how their attitudes may or may not have shifted after training and involvement in the trial, affecting uptake. A questionnaire will be sent to all trial occupational therapists working in rehabilitation pre-and post-implementation of the intervention. Questions seek to explore occupational therapists' beliefs about discharge planning and the work they do with inpatient stroke survivors who will be discharged to the community (home environment) at the end of their program. Respondent demographics will be collected and questions will elicit perceptions of discharge planning and patient participation post-discharge. Additionally, pre-discharge occupational therapy home visit practice and beliefs, as well as barriers and enablers of providing discharge planning support to stroke survivors during rehabilitation will be explored. The second questionnaire distributed at the end of the trial will contain additional questions about the HOME trial, including experiences and satisfaction with the trial, perceived impacts, benefits and challenges, and any site-specific issues. The survey is based on the objectives of the

TABLE 1 Quantitative and qualitative methods of process evaluation data collection employed in the evaluation.

Stage of trial	Data collected
Pre-implementation	- Records of engagement meetings with staff at participating sites - Meetings with occupational therapy managers and rehabilitation physicians to understand service context and service models for discharge planning after first stroke - Descriptions of the organizational characteristics of services using face-to-face interviews, observation and notes from site visits - Survey of all occupational therapists (beliefs about occupational therapy discharge planning) - Participant baseline data across primary and secondary outcomes
Recruitment	- Site screening, eligibility and recruitment log (includes reasons for ineligibility or non-participation) to report participant recruitment and retention as per CONSORT. - Site bed numbers and average length of stay to report representativeness of site - Participant hospital length of stay, age, and stroke severity to report representativeness of participants
Implementation	- Intervention provider details (includes expertise, background and specific training provided) to report against TIDieR checklist - Fidelity monitoring checklists for all components of the intervention completed at participating sites for each intervention provider annually - Diary of co-rehabilitation intervention information (including use of community services, hospital readmission and healthcare resource utilization data from time of discharge to end of 12 months) - Intervention documentation per participant, including session number and length, mode of delivery, session goals, activities completed, equipment/materials provided and trial protocol variation records - Costs of delivering the intervention - Records of meetings with key staff across trial (site coordinators, occupational therapists, consumer engagement panel, trial management committee, data safety and monitoring committee)
Post-intervention	- Participant end of intervention (4-weeks post discharge) and follow-up (6-months post discharge) across primary and secondary outcomes - Post-intervention readmission and healthcare resource utilization, including pharmaceutical and cost data - Caregiver burden at post-intervention (4-weeks post-discharge) and follow-up (6-months) - Face-to-face or telephone interviews with participants, carers and occupational therapists who participated in the intervention - Survey of all occupational therapists (beliefs about occupational therapy discharge planning) - Organizational survey (12-months following final participant recruited) to report maintenance of trial intervention elements

CONSORT, Consolidated Standards of Reporting Trials; TIDieR, Template for Intervention Description and Replication.

trial and process evaluation, as well as previous work. Responses will be rated on a 6-point categorial scale of agreement and obtained through short answer questions. A printed and electronic copy of the questionnaire will be provided to all trial occupational therapists to maximize response rates. Analysis will focus on both perceived acceptance of the intervention and any shifts in beliefs that occur after training and involvement in the HOME Rehab trial.

The 'implementation' dimension of the process evaluation aims to describe the HOME rehabilitation intervention as delivered in terms of quality, quantity, adaptations and variations (planned and unplanned). To assess program fidelity to the protocolized intervention and other factors that may impact the outcome, we will audit the trial documentation, training records, fidelity scoring records, and trial protocol variation sheets. Using descriptive statistics to report the findings, these audits will provide insights into how the planned intervention was implemented.

To explore the 'maintenance' dimension, we aim to examine the long-term individual and organizational impacts of the intervention and understand the extent to which its delivery was normalized among the healthcare professionals and related practice staff. Twelve months post completion of the trial, the lead investigator will survey each site principal investigator to understand which, if any, elements of the HOME Rehab intervention are used, and if so, how they are integrated into usual discharge planning practices at the site.

2.4 Patient and public involvement

Collaborative engagement with stroke survivors, clinicians and policymakers has ensured consumer and community involvement in the design of this process evaluation. The HOME Rehab trial is supported by an end-user advisory panel, inclusive of advisors living with stroke, carers, occupational therapists, health managers and policymakers, who meet on a regular basis; this panel has reviewed all participant-facing documents and will be invited to review emergent themes to ensure involvement through to dissemination. All advisory panel members are paid an honorarium.

2.5 Data analysis

2.5.1 Quantitative data

Quantitative data from clinician surveys, trial logs and fidelity checklists will be entered into a password protected database and will be analysed in SPSS using appropriate descriptive and inferential statistics. Analysis will focus on variability across groups, while the extent to which the intervention is delivered as intended will be examined by exploring the proportion of the essential components which was reported as delivered. Variability in the extent to which the HOME Rehab intervention is delivered as intended across sites and

change across the duration of the trial will also be examined. Program reach will be assessed by examining the proportion of inpatient with stroke who are admitted to recruiting rehabilitation centers and who are recruited to, and engage with, the HOME Rehab trial.

2.5.2 Qualitative data

For qualitative data analysis interview transcripts will be read several times in their entirety independently by two persons. Codes will be developed based on the conceptual framework offered by RE-AIM, with additional thematic findings identified inductively through the data added to the coding framework. Data will be coded within NVivo 12 (QSR International, Doncaster) and thematically analysed using thematic analysis (22). Potential themes will then be reviewed and refined based on their response and relevance to the research questions. Final themes and subthemes will be determined by discussion between the analysts in consultation with the project team (23). Multiple processes will ensure a reflexive stance throughout data collection and analysis. Regular meetings between the interviewer, a second coder (to ensure nuanced and insightful code development) and two project team members experienced in qualitative analysis will hold reflexive discussions of data interpretation, and a range of perspectives. Enhancing trustworthiness of the analysis, discussion will occur about how researcher assumptions may affect the analysis and examination of alternative interpretations and explanations will be undertaken (24). Strengthening dependability and credibility of the analysis, regular project meetings and presentation of potential themes to peers and stakeholders will ensure the themes reflect a convincing account of the dataset (24). A reflexive journal and detailed records will be kept to document a transparent decision trail of analytical and methodological decision making and data interpretation (25). Further, the dataset will be examined for disconfirming evidence that did not support interpretations (24).

2.5.3 Synthesizing data

The integration of findings from multiple data sources will be an important step in refining the interpretation of outcomes, understanding the context of program delivery, and identifying key findings. Results from the qualitative and quantitative methods will be interpreted together using the RE-AIM framework, and areas of convergence or divergence in the findings noted (21). Integrating the findings from multiple perspectives and methods will strengthen the overall findings and provided detailed insights into the causal mechanisms (as proposed in the logic model Figure 1).

3 Discussion

The HOME Rehab trial has been designed to address known challenges with transitioning from an inpatient rehabilitation center to the home environment, and this proposed process evaluation will examine these causal mechanisms as well as the contextual factors that may influence intervention outcomes. The proposed method will provide opportunity to understand the complexity of the HOME Rehab intervention in an iterative manner, while offering a structure to this process so as to ensure past criticisms of process evaluations whereby process evaluations that are conducted ad-hoc or appear to be an afterthought (26) are addressed. Designing the HOME Rehab trial process evaluation as a nested study has ensured that the causal assumptions underpinning the intervention can be tested, and that findings will identify what elements work, when, and in what context (4, 5). We acknowledge that within complex intervention trials, an all-encompassing process evaluation is not possible, instead this process evaluation protocol has identified the key uncertainties held about the interventions and responses to and interactions with the interventions. A potential limitation of this pragmatic approach is that aspects which do not have a substantial influence on the HOME Rehab intervention may have been missed. However, monitoring and evaluating the processes and procedures involved in conducting the trial will enable timely feedback and opportunities for improvement that can help to optimize the study's outcomes and impact in real-time (6). Additionally, knowledge about how an intervention is implemented, its mechanisms of impact, and the contextual factors that impact on the intervention, provides details for scale up and replication in different settings should the program be effective (5).

3.1 Trial status

The HOME trial commenced in 2017, but has encountered multiple delays with restrictions related to the COVID-19 pandemic. Recruitment is ongoing and the trial is expected to be completed in 2024, with final data collection completed in 2025. The process evaluation is embedded within the trial, and therefore conducted across the same time-period.

4 Ethics and dissemination

This study received ethics approval from the Alfred Human Research Ethics Committee under the Australian National Mutual Acceptance Scheme (NMA17/236) and site-specific ethics approval has been obtained at all participating sites. Separate participant information and consent forms were signed for all process evaluation interviews by participants (stroke survivors, carers, stroke clinicians and trial occupational therapists).

Results of the process evaluation will be submitted for publication in peer-reviewed journals and presented at selected, relevant conferences. Use of the RE-AIM framework will provide a comprehensive approach to the process evaluation and the expected outputs and outcomes from the trial and process evaluation are shown in the logic model of the HOME Trial (Figure 2).

Understanding the extent the complex HOME rehabilitation intervention was implemented as intended will support interpretation of the outcomes, and make transparent the factors that impacted on its implementation. Further, knowledge of contextual factors, barriers, as well as which elements of the intervention are perceived to be most useful has important implications for effectively delivering comprehensive discharge planning and support after stroke. Knowing the mechanisms of impact that lead to the final outcomes will enable the intervention to be effectively adapted (if necessary), scaled-up (if effective) and applied in practice with appropriate policies. Trial

training materials will be shared electronically with participating sites, and following trial completion, will be made available on request.

Author contributions

SR: Methodology, Writing – original draft, Writing – review & editing. MS: Methodology, Writing – review & editing, Conceptualization, Data curation, Funding acquisition. LJ: Methodology, Writing – review & editing. NL: Methodology, Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Resources, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Influence of nutritional status on rehabilitation efficacy of patients after stroke—a scoping review

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Stroke patients are susceptible to malnutrition as a result of dysphagia, neurological impairments, and altered levels of consciousness. The nutritional status of individuals post-stroke is a critical determinant influencing the efficacy of rehabilitation outcomes. Therefore, there is great interest in the possible role of nutrients in promoting recovery after stroke. This article examines the enhancement of rehabilitation outcomes through the improvement of nutritional status. A comprehensive literature search was conducted using the PubMed, Cochrane, Web of Science, and Embase databases. Articles relevant to this topic, published from the inception of each database until November 2024, were identified. The selection was restricted to randomized controlled clinical trials, irrespective of language or publication date. The search specifically targeted studies involving stroke patients, encompassing both hemorrhagic and ischemic types, and interventions that combined nutritional supplementation with rehabilitation therapy. Studies with a focus on stroke prevention were excluded. Full-text articles that met the inclusion criteria were retrieved from the aforementioned sources. In instances where both a full report and a conference abstract were available for the same study, only the full report was considered. A total of 751 studies were considered for inclusion in this scoping review. Following a rigorous screening process, 13 studies were selected for detailed analysis. All selected studies were randomized controlled clinical trials. The findings indicate that supplementation with nutrients such as proteins, vitamins, essential amino acids, and antioxidants can enhance activities of daily living, improve balance function, and reduce neurological deficits in post-stroke patients. This review aims to synthesize current evidence regarding the effects of various nutrients and dietary regimens on limb rehabilitation in post-stroke patients, with the goal of providing new insights to facilitate the accelerated recovery of this population.

KEYWORDS

proteins, vitamin D, essential amino acids, antioxidants, nutritional supplement, rehabilitation, stroke

1 Introduction

Globally, one in four people will have a stroke in their lifetime, making strokes the second most common cause of death and the third most common cause of disability (1, 2). Since 2015, stroke has become the leading cause of death and disability in China. As a major chronic non-communicable disease, it poses a serious threat to national health. Over the past decade, stroke prevalence, recurrence, and mortality in China have steadily increased (3).

According to Global Burden of Disease (GBD) data, the prevalence of ischemic stroke in China increased from 1,100 per 100,000 individuals in 2010 to 1,256 per 100,000 individuals in 2019. The 12-month stroke recurrence rate among stroke survivors was reported to be 5.7%. The

"China Health Statistics Yearbook 2020" indicates that the crude mortality rate of stroke in China in 2019 ranged from 129.41 to 158.63 per 100,000 individuals (3). The average age of stroke patients in China is approximately 65 years, which is notably lower than the average age of around 75 years in developed countries (4). Additionally, malnutrition is prevalent among elderly Chinese stroke patients and is associated with increased mortality (5). Malnutrition negatively impacts the rehabilitation outcomes of patients recovering from stroke and hinders the enhancement of their daily living abilities. Addressing malnutrition is essential for stroke recovery, as improving nutritional status may contribute to the rehabilitation process. Nevertheless, a direct causal relationship between nutritional status and rehabilitation efficacy has yet to be definitively established. To investigate whether enhancing the nutritional status of post-stroke patients could potentially improve rehabilitation outcomes, we conducted this scoping review.

1.1 Stroke patients at risk of malnutrition

Studies have found that both acute stroke patients and stroke survivors have certain nutritional risks and deficiencies. Based on the third national stroke registry data, 1.95 to 5.89% of acute stroke patients in China had moderate to severe malnutrition risk. The risk of malnutrition in acute stroke patients is associated with an increased risk of long-term death and severe disability (6). A randomized controlled trial (RCT) involving 323 participants demonstrated that the incidence of anemia among stroke patients during the recovery phase was 42.4%. Additionally, the incidence rates of total protein, albumin, and prealbumin levels falling below normal were 8, 17, and 31.9%, respectively (7). These findings indicate that stroke patients experience significant nutritional deficiencies. Furthermore, a meta-analysis encompassing 915 subjects revealed that malnutrition is particularly prevalent in patients with ischemic stroke and is independently correlated with an elevated risk of stroke-related pneumonia (8).

1.2 Stroke patients with malnutrition may have a poor prognosis

Malnutrition is an independent risk factor for poor prognosis in stroke patients (9). There are many problems associated with malnutrition, including imbalances in energy, protein, vitamins and minerals, loss of self-care ability, prolonged hospitalization, poor functional prognosis, and increased mortality (10, 11). Gomes et al. (12) determined that the risk of malnutrition, as assessed by the Malnutrition Universal Screening Tool (MUST), serves as an independent predictor of mortality, service level, and hospitalization costs within 6 months post-stroke. The most apparent manifestation of malnutrition is weight loss. Specifically, a weight reduction exceeding 3 kg following a stroke significantly elevates the risk of mortality in both the short and long term. Early intervention in such cases can substantially enhance clinical outcomes for patients (13). Nishioka et al. (14) conducted a cross-sectional survey involving 178 stroke recovery patients aged 65 and above, revealing that the enhancement of nutritional status in elderly stroke patients experiencing malnutrition during the recovery phase is associated with significant improvements in daily living activities. Similarly, in patients experiencing acute stroke, malnutrition has been found to be negatively correlated with activities of daily living (ADL) (15).

The extent of neurological deficits following a stroke is positively correlated with the degree of subsequent nutritional deterioration. This decline in nutritional status impedes neurological recovery, elevates the incidence of complications, increases hospitalization costs, and extends the duration of hospital stays (16). A RCT study (n = 277) found that the Geriatric Nutrition Risk Index (GNRI) score at admission was closely related to the neurological function 3 months after stroke. The higher the GNRI nutritional risk level, the worse the neurological prognosis in the recovery period (17).

1.3 Stroke patients' risk factors for malnutrition

Numerous risk factors contribute to malnutrition in stroke patients, including swallowing disorders, neurological deficits, impaired consciousness, advanced age, female sex, pre-existing malnutrition, suboptimal family conditions or inadequate care, the presence of malignant tumors, delayed initiation of rehabilitation, and a history of severe alcoholism (18–20). Additionally, factors such as polypharmacy, feeding difficulties, chronic diseases, functional impairments, and elevated National Institutes of Health Stroke Scale (NIHSS) scores at admission are correlated with an increased risk of malnutrition in this patient population. Dysphagia is identified as the primary risk factor for malnutrition in patients who have experienced a stroke (12).

2 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews statement was followed to report in this study.

2.1 Search strategy

An exhaustive search of the literature was conducted by a medical librarian (FWH) in the Cochrane Library, Ovid Embase, PubMed and Web of Science Core Collection databases to find relevant articles published from earliest database record to 25 November 2024. Databases were searched using a combination of controlled and free text terms for Strokes/Cerebrovascular Accidents, Nutrients, rehabilitation. Randomized controlled clinical trials were exclusively selected for inclusion, regardless of the language or date of publication.

2.2 Study selection

Citations from all databases were imported into the Endnote 20 library (Clarivate Analytics, Philadelphia, PA, United States). Two reviewers (CH and FCH) meticulously evaluated the collected titles and structured abstracts based on predefined criteria. The search was confined to studies involving patients who had experienced a stroke, encompassing both hemorrhagic and ischemic types, and interventions that integrated nutritional supplementation with rehabilitation therapy. Studies focused on stroke prevention were excluded. Complete articles that satisfied the selection criteria were

obtained from the aforementioned sources. No exclusion criteria were applied regarding language or year of publication. In instances where both a full report and a conference abstract were available for the same study, only the full report was included. The suitability of articles for the final review was determined by two reviewers, with any disagreements resolved through consultation with a third reviewer (ZH). The selection process was guided by a PRISMA flow diagram (Figure 1).

Our search initially identified 751 titles. Following the removal of duplicates, 681 studies underwent detailed examination. From these, 36 reports, comprising both articles and abstracts, were selected for further consideration, and ultimately, 13 randomized controlled clinical trials were included in the final review. Three reviewers (CH, FCH, FWH) extracted and summarized the data into a table (Table 1).

3 Results

Patients with ischemic stroke exhibit a high prevalence of malnutrition or are at significant risk for developing malnutrition. It is imperative to conduct nutritional risk screening and initiate early intervention promptly upon hospital admission. Emphasis should be placed on the nutritional management and support of these patients (16). Numerous randomized controlled trials (RCTs) have shown that providing nutritional support to stroke patients can significantly improve rehabilitation outcomes, such as improving limb mobility and cognitive levels in post-stroke patients, reducing infection risks, and NIHSS scores.

3.1 Protein

Whether protein supplementation can enhance neurological recovery in patients with subacute ischemic stroke, a randomized controlled trial (RCT) was conducted. The study randomly assigned diet-independent ischemic stroke patients to either a 21-day protein supplementation group ($n = 20$) or a natural diet control group ($n = 21$). Neurological recovery was assessed using the National Institutes of Health Stroke Scale (NIHSS). The findings indicated that increased protein intake was associated with a reduction in NIHSS scores among post-stroke patients (21). Another RCT showed that malnourished stroke patients receiving enhanced nutritional supplementation had improved motor function (total

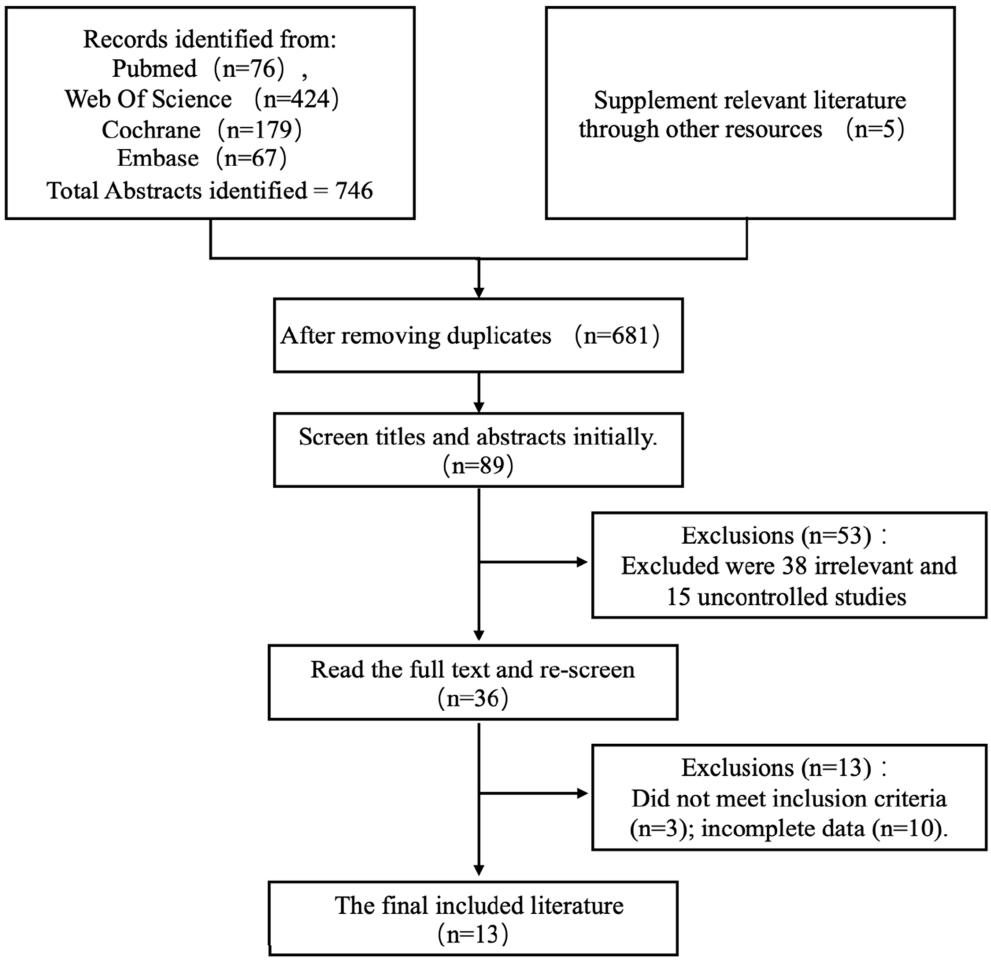

FIGURE 1
PRISMA flow chart diagram describing the study selection process.

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TABLE 1 Summary of studies reporting the effects of nutritional supplements on rehabilitation outcomes in stroke patients.

Authors, Year	Design	Nutritional supplement	Number of participants	Age (years)		Stage of stroke	Rehabilitation program	Duration of intervention (week)
				Intervention	Control			
Aquilani R et al., 2008 (21)	RCT	Protein	41	71 ± 6.9	68 ± 9.1	Acute phase	Standard rehabilitation therapy consisting of proprioceptive neuromuscular facilitation (90 min/day over 5 days weekly).	3
Rabadi MH et al., 2008 (22)	RCT	Protein	116	75.0 ± 10.9	73.6 ± 13.0	Subacute phase	Rehabilitation therapies (physical, occupational, speech)	2
Cheng YH et al., 2020 (23)	RCT	Protein	18	58.8 ± 7.1	56.8 ± 10.1	Recovery phase	Alongside regular PT and OT, three weekly 40 min cycling ergometry training.	8
Sakai K et al., 2019 (24)	Meta-analysis of 8 RCTs	Protein	5,484	–	–	Subacute and recovery phase	Routine rehabilitation protocols (Not specifically described)	
Aylin Sari, 2018 (25)	RCT	Vitamin D	67	69.8 ± 10.1	66.9 ± 10.1	Recovery phase	Rehabilitation therapies (physical, occupational, speech)	12
Shuba Narasimhan, 2017 (26)	RCT	Vitamin D	60	62	65	Not described	Routine rehabilitation protocols (Not specifically described)	12
Momosaki R et al., 2019 (27)	RCT	Vitamin D	97	67.6 ± 11.7	65.5 ± 11.7	Recovery phase	Routine rehabilitation protocols (Not specifically described)	8
Torrisi M et al., 2021 (28)	RCT	Vitamin D	19	59.20 ± 11.4	62.1 ± 10.8	Recovery phase	Motor modules included four daily rehabilitative sessions, 6 days a week, lasting about an hour each. Cognitive rehabilitation included daily sessions based on exercises focused on enhancing attention and memory abilities	12

(Continued)

TABLE 1 (Continued)

Authors, Year	Design	Nutritional supplement	Number of participants	Age (years)		Stage of stroke	Rehabilitation program	Duration of intervention (week)
				Intervention	Control			
Honaga K et al., 2022 (29)	RCT	Vitamin D	50	64.2 ± 8.9	61.3 ± 11.5	Recovery phase	Routine rehabilitation protocols (Not specifically described)	16
Yoshimura Y et al., 2019 (31)	RCT	Essential amino acid	44	80.8 ± 7.1	78.9 ± 6.3	Recovery phase	Rehabilitation therapies (physical, occupational, speech)	8
Ikeda T et al., 2020 (32)	RCT	Essential amino acid	46	65.5 ± 13.1	67.5 ± 5.0	Not described	Each training session includes PT and OT for 20 min each, 2 training sessions per day for 2 months	8
Aquilani R et al., 2009 (35)	RCT	Antioxidant	26	72.0 ± 6.5	74.0 ± 8.0	Subacute phase	Routine rehabilitation protocols (Not specifically described)	4
Garbagnati F et al., 2009 (37)	RCT	Antioxidant	72	61.4 ± 13.6	68.5 ± 12.6	Subacute and recovery phase	Individual physiotherapy began within 24 h of admission, lasting 60 min twice daily (once on Saturdays), 6 days a week. After discharge, patients continued with home or outpatient rehab, attending three 1 h sessions weekly.	48

*All patients in all groups received intervention on the basis of routine spontaneous alimentation.

Functional Independence Measure (FIM) scores, FIM motor subscores, 2 min and 6 min timed walk tests, all significant $p < 0.002$) compared with patients receiving standard supplementation; however, there was no improvement in cognitive measures (FIM cognitive score) (22). Similar findings were reported in another RCT, which indicated that aerobic exercise training combined with protein supplementation can significantly enhance balance and motor coordination in stroke patients, as well as improve their daily living abilities (23).

A meta-analysis (RCT = 8, $n = 5{,}484$) published in 2019 demonstrated that, in comparison to rehabilitation alone, the integration of high-energy, high-protein dietary supplementation with rehabilitation significantly reduces the risk of infections, including pneumonia. However, this intervention did not yield a significant improvement in activities of daily living (ADL) (24). Further research, comprising more extensive and higher-quality randomized controlled trials, is necessary to elucidate the effects of protein supplementation on the rehabilitation outcomes of post-stroke patients (Table 2).

3.2 Vitamins D

Researchers suggest vitamin D supplements aid stroke recovery, with low levels linked to worse outcomes. An RCT study split ischemic stroke patients with low vitamin D into two groups: one received 300,000 IU vitamin D injections, the other got saline injections. Over 3 months, their recovery was assessed using the Brunnstrom Recovery Stage, Functional Walking Scale, Modified Barthel Index, and Berg Balance Scale. The results indicated that vitamin D supplementation significantly improved patients' Berg Balance Scale and Modified Barthel Index scores compared to the control group, but had no significant impact on the Brunnstrom Recovery Stage or Functional Walking Scale. This suggests that vitamin D enhances balance and activity levels but does not affect walking or motor recovery (25). Another RCT study showed that Vitamin D supplementation can significantly improve SSS scores, reduce neurological deficits, and promote recovery in patients after a stroke. Furthermore, another RCT indicated that vitamin D supplementation can significantly enhance Scandinavian Stroke Scale

TABLE 2 Impact of protein supplements on stroke patient rehabilitation.

Authors, Year	Intervention measure		Duration of intervention (week)	Outcome measures	Conclusions
	Experimental	Control			
Aquilani R et al., 2008 (21)	Daily intake of protein-rich supplement (250 Kcal energy, 20 g proteins, 28 g carbohydrates and 7 g lipids)	Blank control	3	NIHSS score▲	Protein supplementation enhances neurological recovery in patients with subacute ischemic stroke
Rabadi MH et al., 2008 (22)	Take the supplement every 8 h (240 calories, 11 g protein).	Take the placebo every 8 h (127 calories, 5 g of protein).	2	FIM total score▲; FIM exercise score▲; 2MWT or 6MWT▲; Discharge rate to home▲; FIM cognitive score	Enhanced nutritional supplementation led to better motor function improvements in patients.
Cheng YH et al., 2020 (23)	Each patient consumed 20 g of a protein supplement (23.2 g protein, 11 g carbohydrates, 144.2 kcal) before and after each training session.	Each patient took 20 g of control supplement (35.2 g carbs, 0.2 g protein) before and after each training session.	8	TUGT; 6MWT; Berg Balance Scale Score▲; LE-FMA; Barthel Index	Aerobic exercise training combined with protein supplementation significantly improves balance in stroke patients
Sakai K et al., 2019 (24)	Energy and/or protein	Placebo or blank control	–	ADL; All-cause mortality; Infection incidence▲	Protein and energy supplementation did not demonstrate a statistically significant impact on activities of daily living (ADL); however, it was associated with a reduction in the incidence of infection.

▲: Indicates a statistically significant difference between the intervention and control groups ($p < 0.05$). FIM, functional independence assessment; 6MWT, 6-minute walking test; 2MWT, 2-minute walking test; ADL, activity of daily living.

(SSS) scores, reduce neurological deficits, and facilitate recovery in post-stroke patients (26).

However, the findings of another multicenter, randomized, double-blind, placebo-controlled trial presented contrasting results. In this study, 100 patients admitted to a rehabilitation ward following an acute stroke were randomly assigned to receive either vitamin D3 (2000 IU/day) or a placebo for 8 weeks. The outcomes indicated that oral vitamin D3 supplementation did not enhance the Barthel index score, Barthel index efficiency, hand grip strength, or calf circumference post-stroke, and had no significant impact on rehabilitation outcomes (27). Additionally, oral vitamin D supplementation did not significantly improve limb function recovery or alleviate depression in post-stroke patients. This was further examined in a 12-week randomized, double-blind, parallel, single-center clinical trial. Participants in the experimental group received a daily oral dose of 2000 IU of cholecalciferol, while the control group did not receive any vitamin D supplementation. Psychological and motor outcomes were assessed through standardized text evaluations. The findings indicated that vitamin D supplementation did not exert a significant impact on mood or functional recovery during the stroke rehabilitation period (28).

Although vitamin D supplementation has not been shown to improve muscle strength and activities of daily living, oral vitamin D supplementation has been shown to inhibit fat infiltration into muscle. A randomized controlled trial (RCT) involving 50 participants examined the impact of nutritional supplementation with whey protein and vitamin D on muscle mass and muscle quality in post-stroke patients. This single-blind, placebo-controlled study allocated the 50 patients into two groups: the high-protein (HP) group received a supplemented jelly containing 100 kcal, 10 g of whey protein, and 20 μg of vitamin D, administered twice daily for up to 16 weeks, while the control group received a placebo jelly. The cross-sectional area (CSA) of the thigh muscle, skeletal muscle index (SMI), muscle strength, activities of daily living (ADL), and some nutritional indicators in the blood were measured. Although there were no significant differences in CSA and SMI between the two groups, fat infiltration of the thigh muscle was significantly lower in the HP group. There were no significant differences in muscle strength and ADL between the two groups. Whey protein and vitamin D supplementation in post-stroke patients can inhibit fat infiltration into muscle (29) (Table 3).

3.3 Essential amino acids

Elevated concentrations of essential amino acids, including glutamate, aspartate, and γ-aminobutyric acid, alongside reduced levels of glycine in plasma, are correlated with unfavorable prognoses following ischemic stroke. This observation indicates that plasma amino acid neurotransmitters may serve as viable targets for

TABLE 3 Impact of vitamins D supplements on stroke patient rehabilitation.

Authors, Year	Intervention measure		Duration of intervention (week)	Outcome measures	Conclusions
	Experimental	Control			
Aylin Sari, 2018 (25)	Upon admission, 2 mL of fluid containing 300,000 IU of vitamin D was injected intramuscularly once	Upon admission, 2 mL saline was injected intramuscularly once	12	BRS; FAS score; MBI score▲; BBS score▲	Vitamin D supplementation boosted activity and sped up balance recovery but did not significantly impact walking or locomotor recovery.
Shuba Narasimhan, 2017 (26)	60,000 IU of cholecalciferol intramuscularly at time of admission	Blank control	12	Scandinavian Stroke Scale (SSS)▲	Vitamin D supplementation can significantly improve SSS scores, reduce neurological deficits, and promote recovery in patients after a stroke.
Momosaki R et al., 2019 (27)	Vitamin D supplementation (2000 IU/day vitamin D3)	Placebo	8	Barthel Index scores; Barthel Index efficiency (Brunnstrom stages; grip strength; calf circumference)	Oral supplementation with vitamin D3 does not enhance rehabilitation outcomes following an acute stroke.
Torrisi M et al., 2021 (28)	vitamin D supplementation (2000IU/day of oral cholecalciferol)	Blank control	12	GSE score; MADRS score; FIM	Vitamin D supplementation does not enhance functional recovery or mood in individuals recovering from a stroke.
Honaga K et al., 2022 (29)	Take supplemental jelly twice daily (100 kcal, 10 g whey protein, 20 μg vitamin D).	Blank control	16	SMI; CSA of the thigh muscles; muscle strength; ADL; Fatty infiltration of thigh muscles▲	Whey protein and vitamin D supplements prevent muscle fat infiltration in post-stroke patients.

▲: Indicates a statistically significant difference between the intervention and control groups ($p < 0.05$). GSE, General Self Efficacy Scale; MADRS, Montgomery Asberg Depression Rating Scale; FIM, functional independence assessment; SMI, skeletal muscle index; CSA, cross-sectional area; ADL, activity of daily living; BRS, Brunnstrom recovery staging; FAS, functional ambulation scale; MBI, modified Barthel index; BBS, Berg balance scale.

intervention aimed at enhancing outcomes in ischemic stroke patients (30). A randomized controlled trial (RCT) was conducted involving an eight-week, two-group parallel intervention with randomized control and blinded outcome assessment in 44 elderly post-stroke patients diagnosed with sarcopenia. The findings indicated that supplementation with leucine-rich amino acids led to significant improvements in Functional Independence Measure (FIM) scores and grip strength among the post-stroke patients. However, there was no significant improvement observed in the skeletal muscle mass index (SMI) (31).

The timing of essential amino acid supplementation may also facilitate recovery. A randomized controlled trial (RCT) examined the effects of the timing of branched-chain amino acid (BCAA) supplementation combined with exercise intervention on physical function in stroke patients. Participants were randomized into two groups based on the timing of supplementation: breakfast ($n = 23$) and post-exercise ($n = 23$). In the breakfast group, supplementation was administered at 08:00, whereas in the post-exercise group, supplementation was provided immediately after exercise between 14:00 and 18:00. In both cohorts, the exercise intervention was administered bi-daily over a two-month period. The findings indicated that the timing of supplementation had a comparable impact on skeletal muscle mass across both groups. However, the ingestion of branched-chain amino acids (BCAAs) at breakfast was particularly efficacious in enhancing physical function and decreasing body fat mass. These results imply that the integration of BCAA consumption at breakfast with a structured exercise regimen is effective in facilitating recovery in post-stroke patients (32) (Table 4).

3.4 Antioxidants

Oxidative stress and inflammation contribute significantly to the cascade of stroke-related malnutrition and ischemic events in the brain. Ischemic damage results in neuronal death and cerebral infarction, which, through intercellular signaling, disrupt the neuroplasticity processes essential for functional recovery facilitated by multidisciplinary rehabilitation therapy. Nutritional interventions incorporating food components with antioxidative and anti-inflammatory properties have the potential to mitigate or prevent

TABLE 4 Impact of essential amino acids supplements on stroke patient rehabilitation.

Authors, Year	Intervention measure		Duration of intervention (week)	Outcome measures	Conclusions
	Experimental	Control			
Yoshimura Y et al., 2019 (31)	Take the leucine-rich amino acid supplement (This supplement contains 3 grams of essential amino acids rich in 40% leucine) once daily.	Blank control	8	ADL▲; SMI▲; HGS▲	Leucine-rich supplements and low-intensity resistance training enhance muscle mass, strength, and physical function in post-stroke sarcopenia patients.
Ikeda T et al., 2020 (32)	A leucine-enriched nutritional supplement (3.5 g of amino acids and 6.5 g of protein, along with 40 IU of vitamin D per 125 mL) provided with breakfast	The same supplement is provided immediately after the workout from 14:00–18:00 in the afternoon	8	Skeletal muscle mass; Leg press strength▲; Grip strength; Body fat mass▲; BBS▲; TUGT; FIM	Consuming a leucine-enriched nutritional supplement during breakfast demonstrates greater efficacy in enhancing physical function and reducing body fat compared to its consumption following rehabilitation exercise.

▲: Indicates a statistically significant difference between the intervention and control groups ($p < 0.05$). ADL, activity of daily living; SMI, skeletal muscle index; HGS, handgrip strength; BBS, Berg balance scale; TUGT, timed up-and-go test; FIM, functional independence assessment.

post-stroke malnutrition. These strategies may be essential for enhancing neuroplasticity, thereby facilitating improved rehabilitation outcomes in stroke patients (33).

Zinc is an essential trace element for human survival. Zinc plays a key role in neuronal proliferation, differentiation, neuronal migration and axonal growth (34). Improving neurological function after stroke through zinc supplementation is a promising therapeutic strategy. A randomized controlled trial (RCT) was conducted to investigate the potential contribution of zinc supplementation to neurological recovery in patients with stroke and low zinc intake. Twenty-six patients with subacute stroke were randomly assigned to either a control group or a zinc supplementation group, with the latter receiving 10 mg/day of zinc. After 30 days of treatment, neurological severity was assessed using the NIH Stroke Scale (NIHSS). The findings indicated that the improvement in NIHSS scores was significantly greater in the zinc supplementation group compared to the placebo group. These results suggest that normalizing zinc intake may enhance neurological recovery in stroke patients with initially low mineral intake (35). The results of animal experiments indicate that injecting the zinc chelator ZnEDTA 14 days after middle cerebral artery occlusion (MCAO) in adult male rats significantly reduced infarct volume and neuronal damage and improved neurological function (36).

A randomized, double-blind, placebo-controlled clinical trial demonstrated that n-3 polyunsaturated fatty acids can reduce the 1-year mortality rate in post-stroke patients. However, these fatty acids did not show significant improvement in neurological function, as measured by the Canadian Neurological Scale (CNS), nor in daily living activities, as assessed by the Barthel Index (BI) and Rivermead Mobility Index (RMI). The study involved the random allocation of 72 patients (47 males; mean age 65.3 ± 12.9 years), who were admitted to a rehabilitation hospital for the sequelae of their first ischemic stroke, into four subgroups. Patients in Group 1 received daily oral antioxidants (including: 290 mg vitamin E, 240 mg vitamin C, 150 mg polyphenols and 19 mg carotene), Group 2 received n-3 polyunsaturated fatty acids, Group 3 received both supplements, and Group 4 received a placebo, all for a duration of 12 months. The results indicated a trend towards a lower mortality rate in the subgroup treated with n-3 fatty acids at the 1-year follow-up ($p = 0.060$). However, there were no significant differences in rehabilitation outcomes, as measured by neurological function (Canadian Neurological Scale, CNS) and activities of daily living (Barthel Index, BI; Rivermead Mobility Index, RMI), between the groups (37) (Table 5).

4 Discussion

Nutritional intervention plays a crucial role in the rehabilitation process for stroke patients. Post-stroke individuals frequently experience malnutrition, which adversely affects their physical health and impedes their rehabilitation progress (38). Consequently, nutritional intervention is essential during the rehabilitation phase. This article elucidates the substantial influence of nutrient supplementation, including protein, essential amino acids, vitamin D, and antioxidants, on the rehabilitation outcomes of stroke patients.

Currently, pharmacological interventions for cerebral infarction primarily focus on enhancing cerebral microcirculation. However, a significant proportion of patients continue to experience varying degrees of neurological dysfunction, including hemiplegia and aphasia (39). While acute thrombolysis has demonstrated efficacy, its application is constrained by a narrow therapeutic window of 3 to 6 h, thereby limiting its availability to a small subset of patients (40, 41). Consequently, the majority of individuals with cerebral infarction are likely to endure persistent neurological impairments.

Hemiplegic stroke can result in a range of muscle abnormalities, characterized by a complex interplay of denervation, disuse, inflammation, remodeling, and spasticity, which collectively lead to

TABLE 5 Impact of antioxidants supplements on stroke patient rehabilitation.

Authors, Year	Intervention measure		Duration of intervention (week)	Outcome measures	Conclusions
	Experimental	Control			
Aquilani R et al., 2009 (35)	10 mg of elemental Zn2+ was given at 10 am daily.	Placebo	4	NIHSS score▲	Zinc supplementation (Zn2+) lowers NIHSS scores and aids neurological recovery in stroke patients.
Garbagnati F et al., 2009 (37)	Antioxidant (290 mg vitamin E, 240 mg vitamin C, 150 mg polyphenols and 19 mg carotene) once daily	Placebo	48	1-year mortality rate▲; Canadian Neurological Scale; Barthel Index; Rivermead Mobility Index	Oral antioxidants do not enhance limb function in post-stroke patients but significantly lower 1-year mortality.

▲: Indicates a statistically significant difference between the intervention and control groups ($p < 0.05$).

phenotypic changes in muscle tissue and atrophy (42). The onset of muscle atrophy following a stroke significantly impedes the patient's rehabilitation process. Research indicates that the muscle thickness and architecture of the lower leg muscles, such as the pennation angle (PA) and fascicle length (FL), are markedly reduced on the affected side compared to the unaffected side in stroke patients. Specifically, the thickness of the soleus and gastrocnemius muscles, as well as the pennation angle of the gastrocnemius, are associated with balance and motor function (43). These findings are corroborated by a meta-analysis (RCT = 15, $n = 375$), which identified stroke-related sarcopenia as a contributing factor to muscle dysfunction on the hemiplegic side (44). High protein intake, particularly through whey protein or branched-chain amino acid supplements, has been shown to significantly enhance skeletal muscle protein synthesis and improve muscle tissue quality. Research indicates that amino acids can mitigate excessive muscle breakdown in post-stroke patients by inhibiting the degradation of myofibrillar protein and skeletal muscle. Supplementation with amino acids can prevent muscle atrophy and facilitate rehabilitation by enhancing physical function, muscle strength, and muscle quality and function (45). It is well-established that therapeutic exercise is frequently employed in exercise rehabilitation programs for stroke patients to enhance physical function. Through structured limb exercises and appropriate activities, patients can improve muscle strength, cardiopulmonary endurance, walking ability, and daily living skills, thereby achieving the goals of injury prevention, functional improvement, and overall health promotion (46). Research indicates that rehabilitation exercise training plays a crucial role in maintaining brain function, enhancing brain plasticity, and increasing resistance to cerebral damage such as ischemia. Prompt and proactive exercise rehabilitation following a stroke has been shown to reduce cerebral infarction volume and ischemia-induced neuronal apoptosis, facilitate the remodeling of corticospinal neurons, and promote axonal growth and dendritic branching, thereby aiding neurological function recovery (47–49). Additionally, some studies have explored the integration of rehabilitation exercise with protein or amino acid supplementation, revealing that such supplementation enhances the adaptive effects and efficacy of exercise rehabilitation (50, 51), which aligns with our findings. Rehabilitation exercise contributes to muscle tissue growth and improved muscle strength. During the rehabilitation phase, protein or amino acid supplementation provides essential substrates for muscle tissue growth, significantly enhancing the efficiency of muscle protein synthesis and improving muscle quality, thus playing a synergistic role in promoting patient recovery.

Patients experiencing residual limb dysfunction post-stroke may exhibit diminished vitamin D synthesis due to prolonged bed rest and limited exposure to sunlight and ultraviolet radiation, rendering them more vulnerable to vitamin D deficiency. Beyond its role in regulating calcium and phosphorus metabolism, vitamin D also exerts numerous non-calcemic effects, including immunomodulation, neuroprotection, oxidative stress inhibition, and the regulation of cellular proliferation and apoptosis (52). The biologically active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), primarily functions through its interaction with the vitamin D receptor (VDR). Research indicates that following cerebral ischemia, there is a significant upregulation of VDR expression in microglia/macrophages surrounding the infarct area. Inactivation of VDR in these cells has been shown to markedly increase infarct volume and exacerbate neurological deficits. Microglia/macrophages deficient in VDR exhibit a pronounced pro-inflammatory phenotype, characterized by the secretion of elevated levels of TNF-α and IFN-γ. Supplementation with $1,25(OH)_2D$, a bioactive form of vitamin D known to activate the vitamin D receptor (VDR), has been shown to effectively enhance VDR expression and suppress the expression of ischemia-induced cytokines such as TNF-α and IFN-γ, thereby mitigating secondary brain damage (53). Additionally, another study demonstrated an association between lower serum levels of $1,25(OH)_2D$ and an increased risk of recurrent stroke in patients with ischemic stroke (54). The present study revealed that, compared to rehabilitation therapy alone, the administration of high-dose vitamin D via intramuscular injection, in conjunction with rehabilitation therapy upon admission, significantly ameliorated neurological deficit symptoms in patients. Conversely, oral administration of low-dose vitamin D combined with rehabilitation therapy did not yield significant improvements in the neurological deficits of stroke patients. Consequently, further research is warranted to ascertain whether varying doses and methods of vitamin D administration differentially impact the amelioration of neurological deficits in stroke patients.

Following a stroke, vascular occlusion resulting from ischemia leads to the excessive production of reactive oxygen species (ROS), with oxidative stress being implicated in exacerbating neuronal damage and contributing to significant functional impairments

(55). Oxidative stress is regarded as a critical environmental factor that adversely impacts neurogenesis by inhibiting all stages of adult neurogenesis (56, 57). This study demonstrates that the combination of antioxidants and rehabilitation therapy can decrease the NIHSS score, ameliorate neurological deficit symptoms, and reduce 1-year mortality rates in post-stroke patients. The potential mechanism underlying these improvements may involve rehabilitation-induced neural structural changes, such as neural sprouting, synapse formation, and dendritic branching (58). Antioxidants, including polyunsaturated fatty acids (such as ω-3 and DHA) and Zn2+, have been shown to mitigate oxidative stress and neuroinflammation, enhance cellular signaling, activate autophagy, and influence growth factors. These compounds facilitate cellular repair and survival by inducing and activating nutritional factors, antioxidant enzymes, DNA repair enzymes, and proteins associated with mitochondrial biogenesis. This process enhances the brain's resilience to more intense stress when exposed to heightened stimulation (59–61). Consequently, the integration of antioxidants with rehabilitative exercise may promote cerebral remodeling and ameliorate neurological deficits following a stroke.

This study investigated the synergistic effects of rehabilitation exercise and nutritional supplementation, including protein, essential amino acids, vitamin D, and antioxidants, on enhancing exercise rehabilitation adaptation and performance. The findings suggest that various nutritional supplementation strategies can facilitate improvements in these areas. Nonetheless, the study has certain limitations. Firstly, the range of nutrients examined is restricted. Future research will aim to assess the impact of a broader spectrum of nutritional supplements on the rehabilitation of stroke patients. Secondly, the study did not address the treatment of dysphagia. Further research is required to develop nutritional supplementation plans and rehabilitation strategies specifically tailored for stroke patients experiencing dysphagia.

Author contributions

HC: Conceptualization, Data curation, Investigation, Software, Writing – original draft, Writing – review & editing. CF: Conceptualization, Data curation, Writing – review & editing. WF: Data curation, Investigation, Writing – review & editing. ZW: Data curation, Methodology, Writing – review & editing. DZ: Conceptualization, Methodology, Writing – review & editing. HZ: Conceptualization, Writing – review & editing, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1502772/full#supplementary-material

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Epineural stimulation on distal brachial plexus for functional restoration of the upper limb in a primate study

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Restoring upper limb function is critical in individuals with central paralysis, and hand control is a priority in patients with neurological impairments. Functional electrical stimulation with implantable electrodes targeting the peripheral nervous system has the potential to selectively recruit hand muscles and generate multiple functional hand movements. However, the implantation of electrodes in the forearm or elbow areas requires multiple incisions for surgery, and elbow joint movements cannot be performed. In this study, we designed and implanted two epineural cuffs on the median and radial nerves in the distal brachial plexus of a single Japanese macaque (*Macaca fuscata*) monkey. The cuffs were successfully placed via an axillary approach using a single incision. Electrical stimuli were applied to innervate the contraction patterns of the hand, forearm, and triceps muscles relevant to the median and radial nerves. The evoked potentials of the target muscles electrically stimulated the distal brachial plexus to reliably and selectively innervate the upper limb muscles at the functional group level. Our results demonstrated that the distal brachial plexus can be a useful stimulation site for upper limb muscle contraction and that the axillary approach enables electrode placement to peripheral nerves required for upper limb control.

KEYWORDS

functional electrical stimulation, peripheral nerve, brachial plexus, epineural, cuff electrodes

1 Introduction

Functional electrical stimulation (FES) is a treatment that involves using mild electrical pulses to muscles or nerves to assist in restoring upper and lower extremity function in individuals who have been paralyzed due to injury to the central nervous system (CNS) (1). Upper limb and hand functionality are particularly important for performing daily activities and increasing the quality of life of individuals with neurological impairments (2). Previous studies have used surface or implantable FES systems in motor neural prostheses to control the arms and hands (3, 4).

Surface FES is more commonly applied clinically during rehabilitation because it is non-invasive. Clinical studies have shown the effectiveness of using surface FES for improving stroke rehabilitation to regain upper limb motor functions (5–7). Innovative technologies, such as flexible multiple-electrode array, have been integrated to generate more selective stimulation (8). However, surface electrodes are applied to the skin and thus have some limitations: they are only suitable for primary muscles close to the skin, have limited ability to selectively innervate individual muscles, require larger currents, and have reverse recruitment

effects leading to fatigue (9). Invasive procedures can be more reliable methods to improve selectivity and performance.

Implantable FES targeting branches of the peripheral nervous system is an alternative strategy for muscle recruitment. Research groups have focused on the median, radial, and ulnar nerves to produce selective functional upper-limb movements. Recent studies have demonstrated the potential of a microfabricated transverse intrafascicular multichannel electrode to selectively recruit extrinsic and intrinsic hand muscles, generating multiple functional grips and hand openings in three monkeys (9). The intrafascicular electrodes are positioned within the nerve fascicles near the efferent axons of different muscles (10, 11) by penetrating both the epineurium and the perineurium. However, needle insertion is associated with increased risks of damage and inflammation. The epineural cuff electrode is another type of multi-contact peripheral nerve interface that has been implemented in clinical neuroprostheses aimed at restoring hand function after paralysis (12, 13). Electrodes are placed on the surface of the nerve to avoid fascicle tissue damage. Precise stimulation can be delivered to a small portion of fascicles, thus enable selective muscle activation.

The brachial plexus is a network of nerve fibers that travels through the posterior triangle of the neck into the axilla. Its anatomical structure allows access to multiple branches of the peripheral nerves and innervates muscles from a single proximal location, reduces the placement of multiple electrodes, and simplifies the surgical procedure (14). In a previous study, we verified the potential for surgical access to the peripheral nerves of the upper extremities using a single surgical approach (15). We successfully implanted epineural cuffs on four peripheral nerves at the brachial plexus level that controlled the upper limbs: the median, radial, ulnar, and musculocutaneous nerves.

In this study, we implanted epineural multi-contact FES cuffs on two peripheral nerves at the proximal level just distal to the brachial plexus and aimed to evaluate their ability to selectively innervate the target muscles of the upper extremity. Approaching all five nerves (median, radial, ulnar, musculocutaneous, and axillary) is possible using a single small axillary skin incision to innervate the entire upper extremity. However, in this study, we focused on stimulating the median and radial nerves because these two nerves innervate the major flexor and extensor muscles of the forearm and hand. Recruitment curves were obtained to quantify the selectivity of the various stimulation parameters for multiple contacts.

2 Materials and methods

2.1 Non-human primate animal model

In this study, we used a single adult male Japanese macaque (*Macaca fuscata*) weighing 10.2 kg. *Macaca fuscata* has an anatomical structure similar to that of humans. The monkey was healthy and exhibited no signs of neurological impairment. The experimental protocol was approved by the Animal Experiment Committee of the Graduate School of Medicine (Approval Number 04-025-000) and the Graduate School of Frontier Biosciences (FBS-22-003-1), Osaka University. All experimental protocols followed the animal research guidelines of the Graduate School of Medicine and Graduate School of Frontier Biosciences, Osaka University, and the NIH guidelines for animal care.

2.2 Epineural cuff

An epineural cuff was developed to validate the ability of the epineural cuff electrodes to innervate the target muscles of the upper limbs. To reduce current spreading and potentially increase the selectivity of the evoked muscles (16, 17), we used a tripolar stimulus configuration. Before confirming the epineural cuff specifications, a neuroanatomical analysis was performed on two cadaver monkeys. This process provides insights into the required diameter of the nerve cuff. A Pt/Ir 90/10 spiral nerve cuff with 3 × 6 contacts, a self-adaptive diameter of 3 mm, and a length of 30 mm was developed by CorTec (GmbH, Freiburg, Germany) (Figure 1B). We also designed a percutaneous connector as an interface between the implanted cuffs and the stimulator (Figure 1C).

2.3 Surgical procedures

Surgery was performed aseptically under general anesthesia with isoflurane (1–3%, inhalation) and continuous monitoring of the monkey's condition and vital signs. After anesthesia, the monkey was positioned supine on the operation table. A 5.5 cm linear skin incision was made from the coracoid towards the humerus on the left upper limb (Figure 1D). Bleeding was carefully stopped using a bipolar coagulator. The deltopectoral groove was blunted to show the brachial plexus, where the nerve fibers could be observed through the translucent connective tissue. The most proximal portions of the median and radial nerves distal to the brachial plexus were freed from the surrounding tissues. Intraoperative electrophysiological stimulation was used to identify the target nerves. Epineural cuffs were gently implanted into the median and radial nerves (Figures 1E,F).

Acute EMG electrode pairs (NE-215B, Nihon Kohden, Japan) were inserted into each target muscle belly, permitting a bipolar electrode configuration with an inter-electrode distance of 10 mm. We chose four flexor muscles in the hand and forearm predominantly innervated by the median nerve and three extensors innervated by the radial nerve (Figure 1G), where finger flexion is produced by the flexor digitorum superficialis (FDS), wrist flexion is achieved by flexor carpi radialis (FCR), finger opposition is performed with first dorsal interosseous (FDI) and opponens pollicis (OP); finger extension is produced by extensor digitorum communis (EDC), wrist extension is achieved by extensor carpi radialis brevis (ECRB), and elbow extension is performed with triceps. A single suture was placed at the entry location on the skin to secure the electrode fixation. Electrical stimulation was used to assist in identifying the target muscles. In addition, a single reference electrode was implanted proximal to the left clavicle. After the experiment, the monkey was awakened and placed in an observation cage under free-moving conditions. Carprofen (3 mg/kg, subcutaneous injection) was used as an analgesic, and ceftriaxone sodium (25 mg/kg, intramuscular injection) was used as an antibiotic.

2.4 Electrophysiology

Electrical stimuli were applied to the epineural cuffs of the monkey under general anesthesia (Figure 1A). During stimulation, we simultaneously recorded compound muscle action potentials (CMAPs) from the seven target muscles (Table 1 and Figure 1G). All

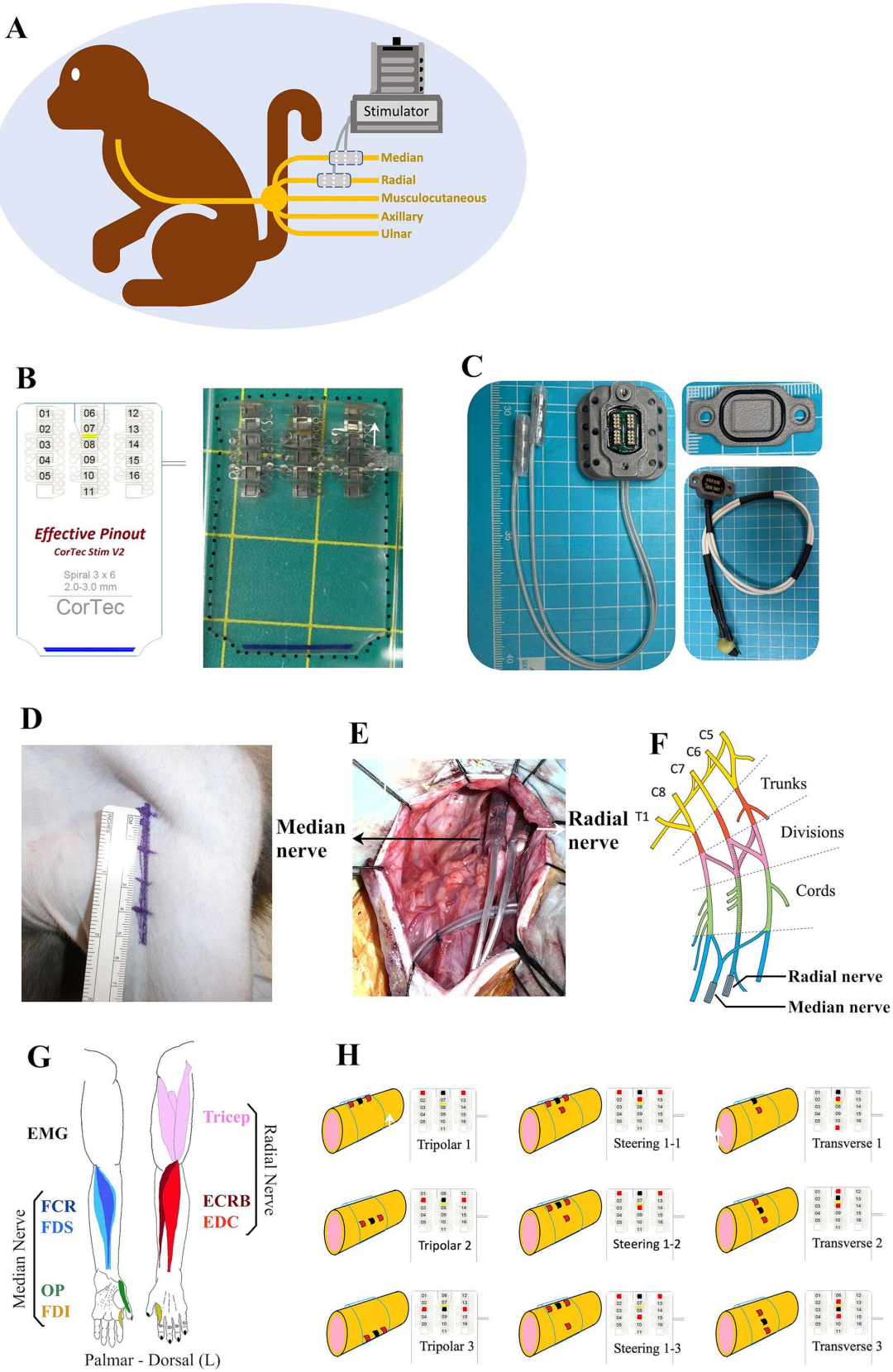

FIGURE 1
Summary of the method employed in this study. **(A)** Monkey with two epineural cuffs implanted on the median and radial nerves ready for stimulation test. **(B)** Schematic practical graph of the custom Pt/Ir 90/10 spiral nerve cuff (CorTec GmbH, Freiburg, Germany), consisting of 3 × 6 electrodes. **(C)** Percutaneous connecter with a sealing cap and a recording cap. **(D)** 5.5 cm skin incision of axillary approach to access the brachial plexus. **(E)** Intraoperative photograph of the implantation of the cuffs. **(F)** Anatomical structure graph showing the position of implanted cuffs. **(G)** Representation of the flexor and extensor muscles of the monkey upper limb innervated by the median and radial nerve. **(H)** Different stimulation configurations showing the positions of cathodes (red spots) and anodes (black spots).

TABLE 1 Muscles for EMG recoding, their functions, and the nerve supply.

Muscles (EMG)	Functions	Nerve supply
Flexor carpi radialis	Wrist flexion	Median N.
Flexor digitorum superficialis	Finger flexion	
First dorsal interosseous	Index opposition	
Opponens pollicis	Thumb opposition	
Extensor digitorum communis	Finger extension	Radial N.
Extensor carpi radialis brevis	Wrist extension	
Triceps	Forearm extension	

stimulations and EMG recordings were performed using a processor unit (RZ2; Tucker-Davis Technologies, United States) and a Subject Interface (SIM10-6, Tucker-Davis Technologies, United States) with Synapse software. Disposable subdermal needle electrodes were connected to a needle electrode adapter (S-BOX16; Tucker-Davis Technologies, United States). EMG activities were collected at a sampling rate of 12,207 Hz and filtered using a 20–500 Hz order bandpass filter.

Electrical stimuli were administered as constant-current charge-balanced cathodic-first biphasic pulses. We used a 32-channel ZIF-Clip headstage (ZC32-P, Tucker-Davis Technologies, United States) to deliver pulses with a pulse width of 150 μs and a frequency of 1 Hz. Across different experimental conditions, we varied the amplitude from 100 μA to 4,000 μA and performed six repetitions of each current step. We employed different stimulation configurations: the traditional longitudinal tripolar, tripolar with steering, and transverse tripolar (Figure 1H). In traditional tripolar stimulation, we utilized five cathodes, whereas in transverse tripolar stimulation, all six cathodes were used. To mitigate the effects of fatigue, we enforced a 1-min rest period between changes in the stimulation cathodes.

2.5 Muscle recruitment and selectivity

Muscle recruitment curves were generated by recording the CMAPs obtained from each target muscle. Data within a 50-ms data window were captured for each stimulation pulse, spanning 10 ms before and 40 ms after the onset of stimulation. This process was set up using Tucker-Davis Technologies Synapse software and performed in real time.

We used the peak-to-peak amplitude of the evoked CMAPs to investigate the relationship between the evoked muscle response and stimulation intensity. The maximum CMAP amplitude recorded for each muscle during the experiment was used to normalize the CMAPs for each muscle separately, thus enabling the production of normalized recruitment curves for each muscle. The selectivity of each muscle was assessed by calculating the selectivity index (SI). SI was calculated using the equation outlined by Badi et al. (9) as follows.

$$SI_m = CMAP_m - \frac{\sum_{n \neq m}^{M} CMAP_n}{M - 1}$$

where m is the muscle of interest, M is the total number of muscles, and CMAP is the normalized CMAP. The SI calculation ranges from −1 to 1, where −1 indicates full activation of all non-target muscles and zero activation of the muscles of interest, and 1 indicates full activation of the target muscle and zero activation of all non-target muscles. All the calculations were performed using MATLAB (MathWorks, 2023a).

2.6 Histological evaluation

Nerve samples from the distal brachial plexus were dissected after transcardial perfusion and embedded in paraffin for histological evaluation. Choline acetyltransferase (ChAT) is used as a marker of cholinergic neurons and specifically labels motor neurons (18). The coronal sections were processed for immunohistochemical staining with Nissl and anti-ChAT antibodies.

The tissues first underwent antigen retrieval treatment for 10 min in sodium citrate buffer (0.1 M citric acid, 0.1 M sodium citrate, pH 6.0) at 121°C. After inactivation of endogenous peroxidase with 3% H_2O_2 in methanol for 15 min at room temperature, the tissues were incubated with primary rabbit anti-ChAT antibody (1:250, bs-0042R, Bioss, United States) overnight at 4°C. After washing with phosphate buffer saline (0.05 M PBS, pH 7.6), the tissue was labeled with peroxidase secondary antibody (424144, Histofine Simple Stain MAX PO; Nichirei, Japan) for 30 min at room temperature. The sections were visualized using 3,3′-diaminobenzidine tetrahydrochloride (Nichirei) at room temperature. Sections were counterstained with Mayer's hematoxylin and examined under a microscope. Images of the sections were captured using a microscope (BZ-X800, Keyence, Japan) at 4× and 40× magnification, manually outlined, and quantitatively measured using BZ-X800 software.

3 Results

3.1 Electrodes implantation

We successfully implanted two cuff electrodes onto the most distal portion of the median and radial nerves just distal to the brachial plexus through the axillary approach with a 5.5 cm skin incision (Figures 1D–F). This approach is applicable and efficient for placing epineural cuffs on up to four nerves that control the entire upper extremity. However, the axillary nerve lies behind the axillary artery and is occluded by the teres major, making it difficult to access (15). Additionally, we investigated the cross-sectional area of fascicles in the implanted area. Our results showed a single large fascicle in the median nerve and one larger-diameter fascicle accompanied by several smaller-diameter fascicles in the radial nerve (Figures 2A,B) harvested from the implanted site (Figure 1F). Immunohistochemical results of ChAT staining revealed a heterogeneous distribution of motor neurons within each fascicle of the median and radial nerves (Figures 2A,B). Chronic electrode impedance measurements demonstrated that the impedance was relatively stable (Figure 2C). The 10% activation threshold of recruitment gradually decreased 1 month after implantation, indicating a stable microenvironment between the electrodes and the nerve surface (Figure 2D). The selectivity index of longitudinal tripolar stimulation over 45 days after implantation (Figure 2E) showed a relatively stable performance of the implants.

3.2 Muscle recruitment and selectivity

Typical contraction patterns of muscles relevant to the innervated peripheral nerves were observed following electrical stimulation of the epineural cuffs. The recorded CMAPs validated that the electrical stimuli on the median and radial nerves innervated all the recorded upper limb muscles. The peak-to-peak response increased until saturation as the amplitude of the stimuli increased from the subthreshold to saturation (Figures 3, 4).

The time delay between stimulus onset and the recorded CMAPs was approximately 6 ms for both the median and radial nerves. This indicates that forearm muscle recruitment was achieved through the direct innervation of motor axons in macaque monkeys (9).

The recruitment curves showed normalized activation of the upper limb muscles during the median (Figure 3) and radial (Figure 4) nerve stimulation in all five tripolar sets. To visually clarify the recruitment order, we focused on the region of the recruitment curves corresponding to the range between the subthreshold and saturation responses. Our results revealed that specificity FDI and OP when stimulating the median nerve, whereas the triceps exhibited an earlier order than ECRB and EDC when stimulating the radial nerve. These results suggest that the proximal muscle groups have lower thresholds than the distal muscle groups when stimulating peripheral nerves at the distal portion of the brachial plexus.

To achieve more selective innervation of the muscles within the same group, we tested different stimulation parameters by changing the configuration and pulse width. Transverse tripolar and steering configurations increased the subthreshold, saturation, and span compared to the longitudinal tripolar configuration and could distinguish the two recruitment curves of muscles from the same group (Figure 5A). More complete figures are provided in the Supplementary Figures 1, 2. The stimulation with a shorter pulse width required a higher amplitude to reach the recruitment threshold (Figure 6). However, the effect of modifying the stimulation configuration and pulse width was limited to the innervation of different muscles in the same group.

Further, we quantified the selectivity of muscle contraction by the three types of tripolar stimulation using SI, a metric that reflects the normalized activation of each muscle with respect to non-target muscles. The maximum selectivity indices for each muscle and the corresponding configuration are outlined in Table 2 and Figure 5B.

4 Discussion

We implanted two customized epineural cuff electrodes onto the most proximal portion of the median and radial nerves just distal to the brachial plexus in a macaque monkey using the axillary approach with a single 5.5 cm skin incision. Electrical stimulation at the distal brachial plexus level demonstrated the ability to selectively innervate the upper limb muscles at the functional group level. Our results highlight the feasibility of distal brachial plexus stimulation for control of the entire upper extremity.

In this study, we validated that the distal brachial plexus can be a useful stimulation site for FES aimed at controlling all upper limb muscles. Previous studies have implanted electrodes on peripheral

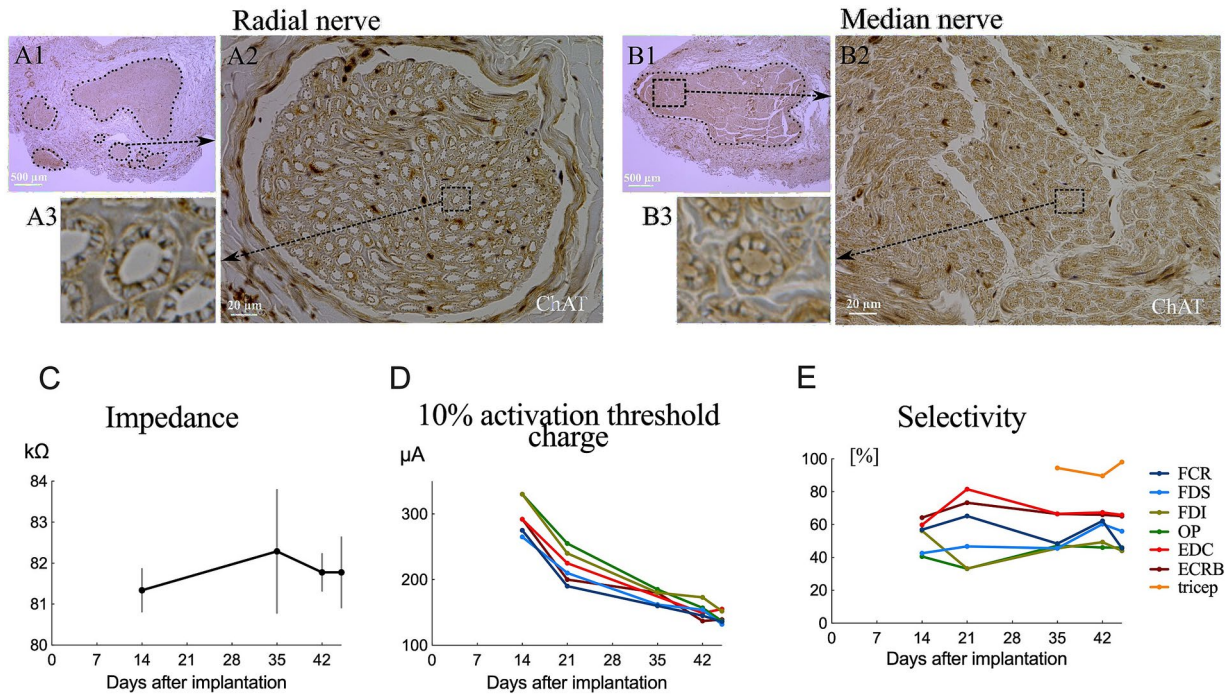

FIGURE 2
Fascicular morphology of the median **(B1)** and radial **(A1)** nerves at the distal portion of the brachial plexus in monkeys. Cross section of ChAT-labeled median **(B2,B3)** and radial **(A2,A3)** nerve showing the mapping of the fascicles (outlined by dotted lines). **(C)** Impedance changes of the averaged results over all electrodes 45 days after implantation. **(D)** Chronic evaluations of the activation charge threshold (10% recruitment). **(E)** Change in selectivity index of tripolar stimulation over 45 days after implantation.

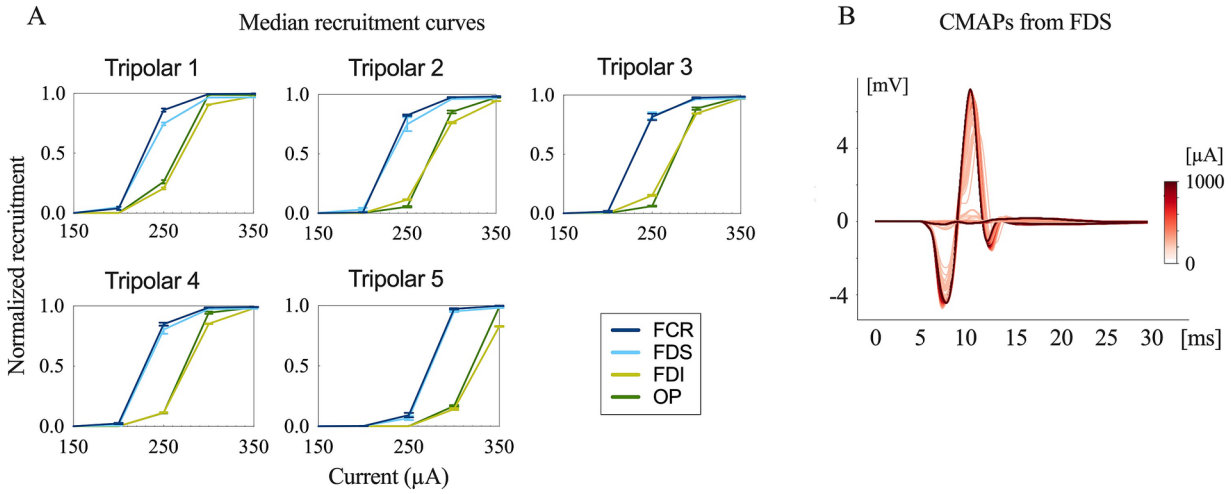

FIGURE 3
Evoked compound muscle action potentials and recruitment curves. **(A)** Recruitment curves for the five longitudinal tripolar configurations obtained during median nerve stimulation. The *x*-axis has been scaled to focus on the transition phase of the subthreshold and saturation region. **(B)** Evoked compound muscle action potentials for the different stimulation amplitudes recorded from FDS (flexor digitorum superficialis) (stimulation onset at 0 ms).

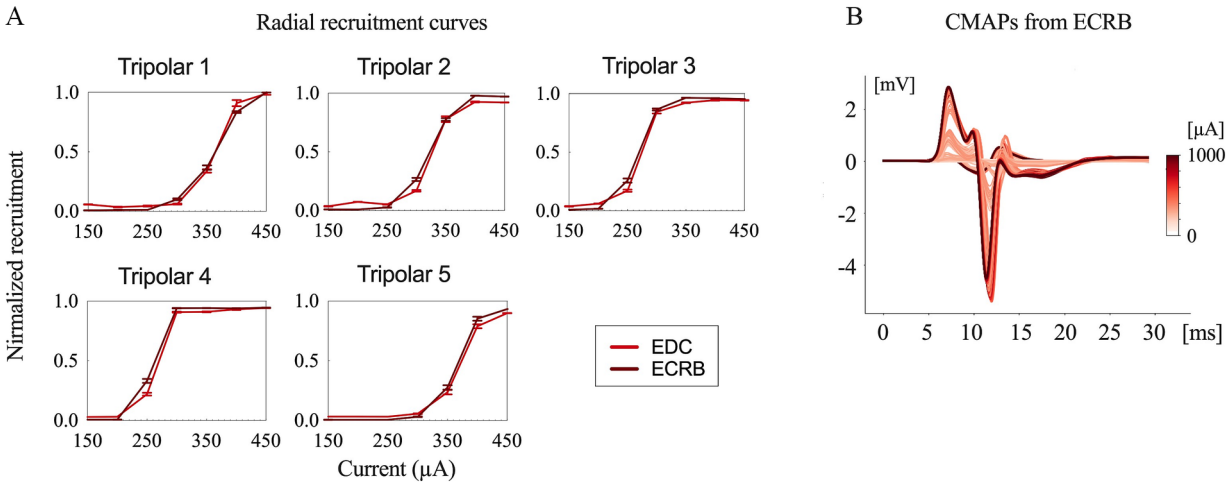

FIGURE 4
Evoked compound muscle action potentials and recruitment curves. **(A)** Recruitment curves for the five longitudinal tripolar configurations obtained during radial nerve stimulation. **(B)** Evoked compound muscle action potentials for the different stimulation amplitudes recorded from ECRB (extensor carpi radialis brevis).

upper limb nerves at different sites (9), usually with median electrodes placed near the elbow and radial electrodes near the epicondyle. However, this strategy requires longer cables between each electrode and connector, complicating the surgical procedure. Moreover, the biceps (musculocutaneous nerve) and triceps (radial nerve) cannot be innervated by stimulating the elbow. One feasible approach to access the musculocutaneous nerve is the axillary approach, which targets the distal branch of the brachial plexus.

The brachial plexus is a network of nerve fibers connecting the cervical roots and the motor and sensory nerves of the upper extremities. This anatomical feature makes it easy to access and place the epineural cuffs on all five peripheral nerves, innervating the upper extremities through a single axillary approach. This highlights the feasibility of producing entire upper-extremity muscle control, including the triceps, which is the principal muscle responsible for elbow extension. The axillary approach is the most popular method of accessing the brachial plexus. Only one small skin incision is required for this approach, thus decreasing the surgical site and simplifying the cabling system of the multi-cuff implantable device.

Epineural recruitment at the distal portion of the brachial plexus was found to engage the intrinsic muscles of the hand and arm and selectively activate a large number of flexor and extensor muscles. Fascicular topography of the arm nerves has shown that, in the fascicles, the deep middle fibers innervate distal muscles and that superficial fibers innervate proximal muscles (19). Our results revealed that lower amplitude stimulation can innervate proximal muscles, and as the

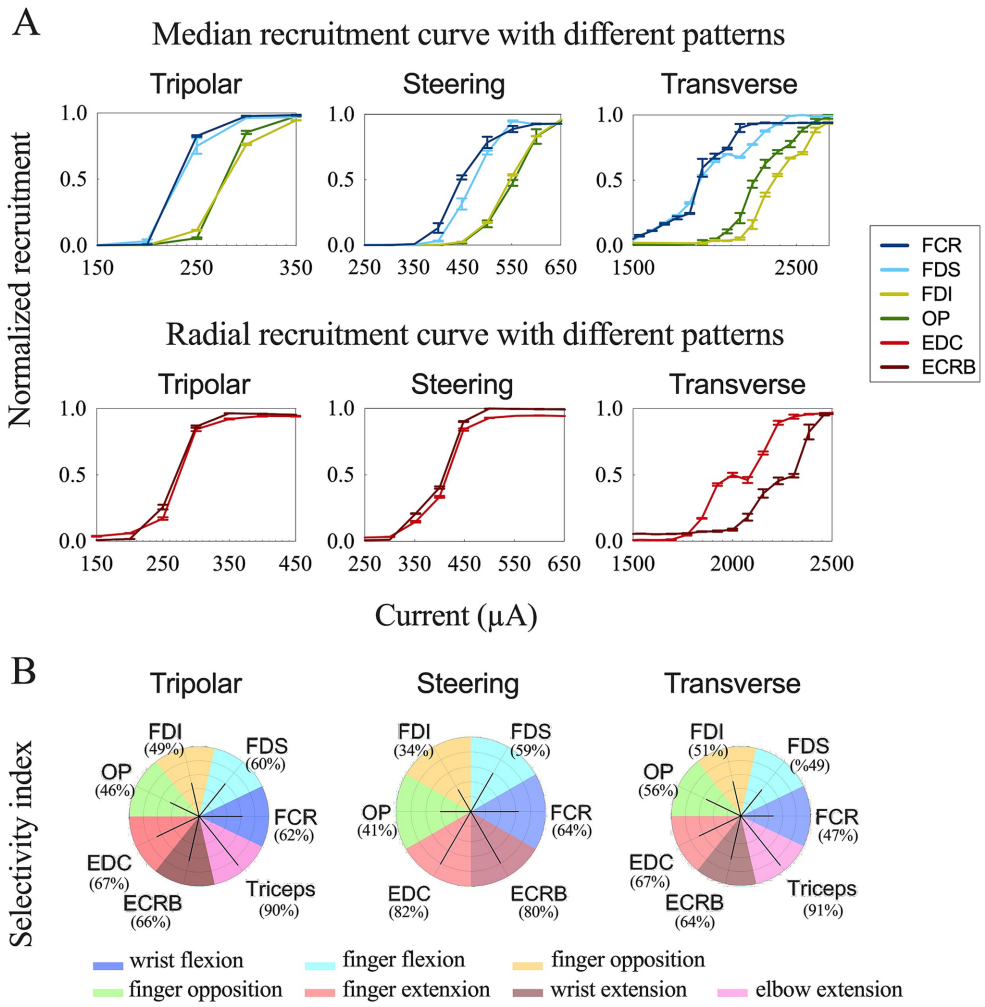

FIGURE 5
Comparison results of different stimulation configurations. **(A)** Recruitment curves for longitudinal tripolar, tripolar with steering, and transverse tripolar stimulating on median (top) and radial (bottom) nerves. **(B)** Summary of selective muscle activation for the median and radial nerves. Selectivity for each muscle was achieved using different stimulation configurations. The dark line represents the selectivity index. The color of each polar plot separates each muscle.

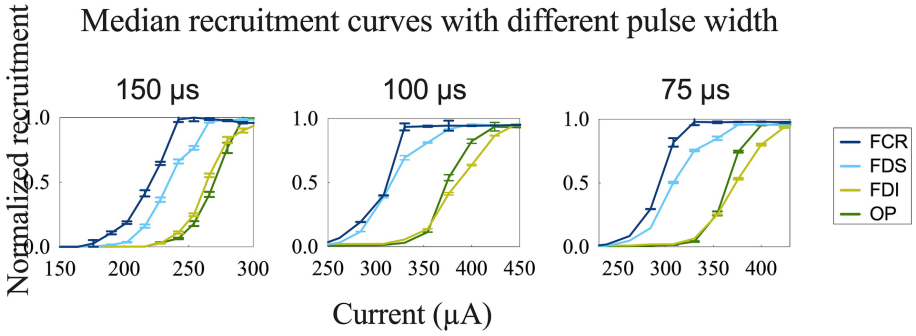

FIGURE 6
Recruitment curves for comparison of different stimulation pulse widths obtained during longitudinal stimulation on the median nerve.

stimulus amplitude increases, deeper fibers are activated, allowing more distal hand muscles to be innervated. Additionally, the stimulation sites of the cathode did not affect the recruitment selectivity. However, we did not differentially stimulate each muscle in the same functional group (for example, the FCR and FDS both innervate wrist flexion). A cross-sectional examination of the motor fiber distribution at the distal

TABLE 2 Maximum selectivity index for the upper arm muscles and the corresponding stimulation protocol.

Muscle	Selectivity index	Configuration	Amplitude (μA)
Longitudinal tripolar stimulation			
FCR	62.19%	Tripolar-3	160
FDS	60.26%	Tripolar-5	192
FDI	49.32%	Tripolar-1	434
OP	46.01%	Tripolar-3	480
ECRB	67.08%	Tripolar-1	2,500
EDC	65.96%	Tripolar-1	1,528
Triceps	89.64%	Tripolar-2	708
Transverse tripolar stimulation			
FCR	46.15%	Transverse-6	2,050
FDS	48.6%	Transverse-3	2,250
FDI	51.35%	Transverse-3	1,950
OP	55.62%	Transverse-3	2,000
ECRB	64.34%	Transverse-5	1,350
EDC	66.86%	Transverse-5	1,850
Triceps	91.31%	Transverse-1	950
Tripolar with steering stimulation			
FCR	64.34%	Steering 5-6	550
FDS	59.49%	Steering 4-5	450
FDI	34.22%	Steering 5-4	1,000
OP	40.94%	Steering 5-3	800
ECRB	79.89%	Steering 5-2	800
EDC	81.65%	Steering 3-1	500

brachial plexus showed one main large fascicle with fewer subfascicles, indicating that it is difficult to selectively match the targeted muscles and specific area of the fibers of the terminal branches. We attempted three different stimulation configurations (longitudinal tripolar, tripolar with steering, and transverse tripolar) with different cathode sites to selectively activate deep fibers; however, the effect was not satisfactory.

Intraneural transverse intrafascicular recruitment at the elbow level produces fine hand movements (9). However, stimulation of the radial nerve at the epicondylar segment cannot activate the triceps, and elbow joint extension cannot be achieved. Our results showed higher maximum selectivity values obtained through epineural stimulation than those obtained using intrafascicular stimulation (9) (Table 2). This may be attributed to the relatively high selective recruitment of epineural stimulation on motor fibers lying near the nerve surface and the relatively weak recruitment on the fibers deep inside the nerve. Additionally, owing to the design of the intrafascicular electrodes, only monopolar stimulation can be applied. A tripolar configuration can achieve better control of the stimulation electric field than a monopolar electrode (20).

Persistent motor impairment in the arm after damage to the CNS due to injury or disease, such as in post-stroke patients and those with incomplete spinal cord injuries, can make patients functionally dependent on others for daily activities. Epineural FES may be a useful tool for inducing the contraction of paralyzed muscles and performing basic joint activities. The functional movement control of the upper limbs in complete paraplegics and tetraplegics remains promising. Stimulation has the advantage of functioning and exercising over a long period (21). Implantable electrodes are placed perineurally to deliver smaller currents on a small portion of fascicles, thus enable more selective activations to target muscles and reduce the occurrence of fatigue (22). Our epineural cuffs were designed to accommodate multiple nerve diameters and not harm the peripheral nerve, thereby extending stable implantation time. Previous anatomical research on the upper limb muscles and nerves in monkeys and humans (19, 23) has revealed that the structure of the arm is preserved in primates, suggesting that our approach in monkeys could be translated to humans.

Sensory fibers were also founded in each fascicle in both median and radial nerves with a heterogeneous distribution (Figures 2A,B). Unwanted activation on afferent sensory fibers can contribute to the evoked muscle contraction by the synaptic recruitment of motor neurons in the spinal cord (H-reflex) (24, 25). However, sensory axons have a longer strength-duration time constant and lower rheobase than motor axons and are more preferentially recruited by wider pulses widths (0.5–1 ms) and lower stimulating amplitudes (26, 27). Our stimulating pulse widths were limited shorter (75 μs, 100 μs, 150 μs), and preferentially activated motor fibers. CMAPs results from EMG recording (Figures 3B, 4B) showed a short onset latency of 5 ms, indicating that the muscular responses were mediated by a direct peripheral pathway and not by transsynaptic Ia-mediated reflex responses (28).

This study has certain limitations. In this early-stage study, we implanted only two cuffs on the radial and median nerves to simplify the experiment. We did not use pharmacological nerve blocks to inhibit the effects of the spinal circuits. The acute EMG electrodes were inserted at slightly different points on each experimental day, resulting in some variance in the selectivity analyses. In future experiments, a chronic EMG recording method is recommended to minimize this influence.

In the next step, epineural stimulation with a higher frequency rather than a single pulse is required to generate functional joint movements. In addition, cuffs were placed on all four nerves (median, radial, ulnar, and musculocutaneous) to test functional movements and tasks. The surgical approach also requires further optimization to reliably access the axillary nerve. In terms of the stimulation method, more stimulus patterns and parameters must be tested to improve the selectivity of the evoked muscles. Fully implantable devices with wireless charging coils and rechargeable batteries are another significant improvement for the long-term implantation of electrodes. For a long-term research plan, the FES effect can be improved by combining it with brain-computer interface technology for motor control. We expect that this study will develop brain-controlled peripheral nerve FES interface research to support upper limb functionality and further benefit humans with neurological impairments.

5 Conclusion

The distal brachial plexus may be a useful stimulation site for functional electrical stimulation using an axillary approach with a single skin incision. Electrical stimulation at the distal brachial plexus level demonstrated the ability to selectively innervate the upper limb

muscles at the functional group level. The stimulation sites on the cathode did not affect the recruitment selectivity. Our results highlight the feasibility of distal brachial plexus stimulation for control of the entire upper extremity.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was approved by the Animal Experiment Committee of the Graduate School of Medicine (Approval Number: 04-025-000) and the Graduate School of Frontier Biosciences, Osaka University (Approval Number: FBS-22-003-1). The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

TY: Writing – original draft, Writing – review & editing, Formal analysis, Investigation, Methodology, Resources, Validation. BF: Conceptualization, Data curation, Methodology, Formal analysis, Software, Writing – review & editing. LL: Data curation, Investigation, Methodology, Writing – review & editing. YL: Writing – review & editing. TK: Methodology, Writing – review & editing. TS: Methodology, Writing – review & editing. MH: Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1515986/full#supplementary-material

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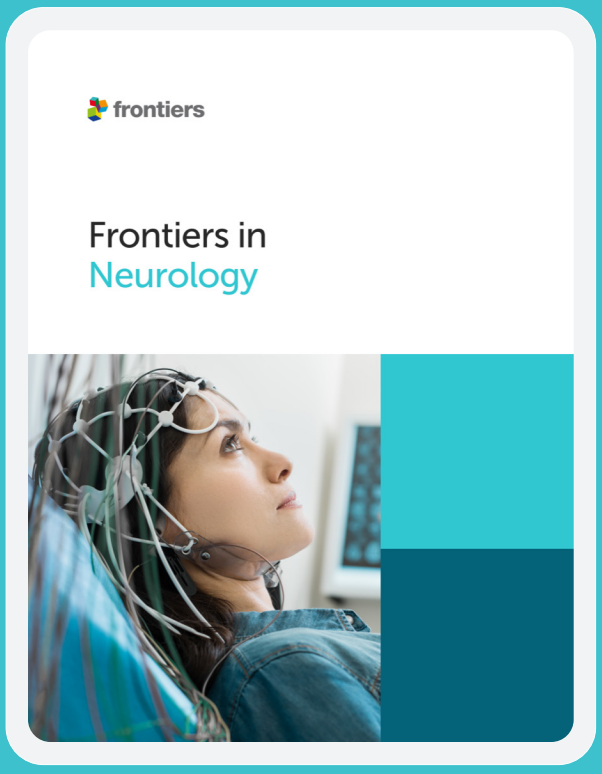

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