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Aging-related changes in auditory perception and cognition: Measurements, mechanisms, and interventions

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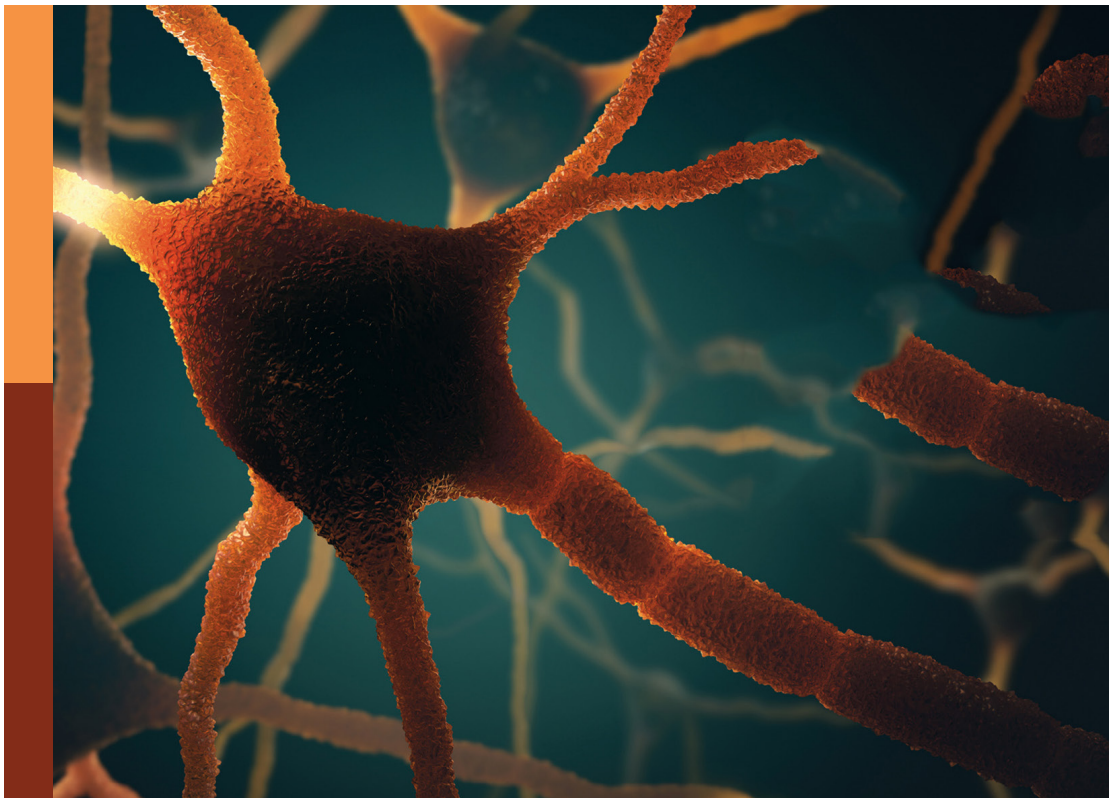

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Aging-related changes in auditory perception and cognition: Measurements, mechanisms, and interventions

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Widowhood Impairs Emotional Cognition Among Elderly

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Background: The negative impacts of spousal bereavement on the emotional health of the elderly (e.g., depression and anxiety) have been revealed. However, whether widowhood impairs emotional cognition among the elderly is less known. The purpose of this study is to reveal the emotional cognitive deficits among the widowed elderly.

Methods: In this study, we recruited 44 widowed elderly (WE) and 44 elder couples (non-widowed elderly, NWE) and examined their emotional cognition including attention and visual working memory, which were measured by the visual search task and delayed-match-to-sample task, respectively. Three kinds of emotional faces (i.e., sad, angry, and happy) were adopted as the attentional or mnemonic targets.

Results: It revealed that WE had a general deficit in search efficiency across emotional types, while they showed mnemonic deficits in negative faces but not positive faces. Furthermore, the modeling analysis revealed that the level of depression or state anxiety of the elderly moderated the effects of widowhood on the deficits of mnemonic processing, i.e., the deficits were only evident among WE with the high level of depression or state anxiety.

Conclusion: These findings reveal the attentional deficits in sad, angry, and happy faces and the mnemonic deficits in sad and angry faces among elderly who suffer from widowhood and point out the important role of emotional problems such as depression and state anxiety in modulating these emotional cognitive deficits.

Keywords: widowed elderly, cognitive deficit, emotional cognition, attention, visual working memory

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INTRODUCTION

Spousal bereavement is a common negative event in later life that negatively influences the mental and physical health of the elderly. The widowed elderly reported increased anxiety, grief, depression, emotional loneliness, and social loneliness (Bergman et al., 2010; Kim and Lyu, 2018; Förster et al., 2019; Szabó et al., 2020). These negative impacts of widowhood were found to last a long period and thus were serious threats to wellbeing and quality of life in the elderly (van Boekel et al., 2019). Although the negative impacts of spousal bereavement on the emotional health of the elderly have been revealed, whether widowhood impairs emotional cognition among the elderly is less known. The purpose of this study is to reveal the emotional cognitive deficits among the widowed elderly.

First of all, emotional cognitions could change with aging. From the perspective of socioemotional selectivity theory, aged ones are motivated to derive emotional meaning from life and adopt an adaptive emotion regulation strategy to maximize the positive affect and minimize the negative affect (Carstensen et al., 1999). Evidence showed cognitive biases to positive emotion among the elderly, e.g., perceiving ambiguous expressions more positive (Kellough and Knight, 2012) and reliable attention to positive stimuli (e.g., happy faces) (Carstensen and Mikels, 2005; Reed et al., 2014; Gronchi et al., 2018). Correspondingly, electrophysiological activities were found higher for pleasant pictures than unpleasant ones among elderly (Pehlivanoglu and Verhaeghen, 2019). In addition to the cognitive bias to positive emotion, the elderly also allocated fewer resources to negative emotions. For example, the elderly showed attentional inhibition and attentional avoidance to negative emotions (e.g., sad and angry faces) (Mather and Carstensen, 2003; Bannerman et al., 2011). Electrophysiological evidence also revealed that angry faces evoked a smaller P1 amplitude in the elderly compared with that in young adults (Mienaltowski et al., 2011). However, it should also be noted that some studies suggested cognitive biases to both positive and negative emotions among the elderly (Smith et al., 2005; Murphy and Isaacowitz, 2008). Furthermore, it was indicated that the attentional bias toward happy faces is an automatic process, and the attentional avoidance of fearful faces is a controlled mechanism (Gronchi et al., 2018). Taken together, aging increases cognitive biases to positive emotions (Carstensen and Mikels, 2005) and possibly decreases the allocation of cognitive resource to negative emotions.

Another factor that may affect emotional cognition could be the emotional state. According to the cognitive-behavioral model, individuals with high anxiety/depression have distorted or dysfunctional cognitive structure-labeled schemas that lead to distorted or biased information processing, which plays a central role in the development and maintenance of depression/anxiety (Beck, 1964, 1967; Rapee and Heimberg, 1997; Turk et al., 2001; Heimberg et al., 2010; Beck and Haigh, 2014). It has been shown that highly anxious individuals showed attentional bias toward threatening faces (e.g., angry faces) (Bradley et al., 1999; Gamble and Rapee, 2010; Liang et al., 2017; Abend et al., 2018), while, individuals with depression showed selective attention to sad faces (Joormann and Gotlib, 2007; Kujawa et al., 2011) and dwell longer on sad faces (Lazarov et al., 2018). Among the aged ones, it also revealed that depressed elderly recognized sad and angry faces better than happy faces (Shiroma et al., 2016; Ferreira et al., 2021), and anxious elderly showed attentional vigilance to sad faces (Lee and Knight, 2009). Therefore, emotional problems such as depression and anxiety may bias the cognition to negative stimuli.

Although the effects of aging and emotional state on emotional cognition have been well studied, the effect of widowhood on emotional cognition among the elderly was rarely examined. On one hand, according to the socioemotional selectivity theory, the elderly might prefer positive emotion. It thus can be hypothesized that the widowed elderly might have cognitive biases toward happy faces. In contrast, according to the cognitive-behavioral model, it can be hypothesized that the widowed elderly might have biased cognition to negative emotions, as the level of anxiety and depression may be higher among them. To reconcile this discrepancy, we conducted behavioral measurements of emotional cognitions between widowed elderly and elder couples. Both attentional processing and working memory processing were examined. Moreover, we explored the moderating roles of depression and anxiety in these cognitive deficits.

Regarding the attentional processing, we adopted the visual search paradigm in which participants were asked to detect, locate, or identify a target among distractors as quickly as possible. The results reveal how attention suppresses irrelevant distractors as well as shifts/orients to the target. The visual search paradigm is a well-established approach in measuring visual attention, which has been pervasively adopted to test emotional attention across adults of different ages (Hahn et al., 2006; Mather and Knight, 2006; Lundqvist et al., 2013; Dodd et al., 2017; Wieser et al., 2018; Suslow et al., 2021). Besides the accuracy and reaction time (RT), the search slope is an important indicator of search efficiency and should also be examined. A search slope is the slope of the fitting line of RT against the size of the search array. A steeper search slope denotes a large increase of the RT with the increase of distractors and inefficiency in searching the target.

Regarding the working memory processing, we adopted the delayed-match-to-sample (DMTS) paradigm, which is one of the most common tasks used to study visual working memory. The DMTS task consists of three phases, namely, a sample (encoding) phase, a delay (maintenance) phase, and a test (retrieval) phase. It is mainly used to examine the accuracy and capacity in encoding and maintaining visual stimuli. Previous studies showed stable test-retest reliability in the DMTS task (Borghans and Princen, 2012) and stable brain structures associated with the task (i.e., dorsolateral prefrontal cortex, fusiform gyrus, and posterior parietal cortex) (Daniel et al., 2016). Most of the studies concerning emotional cognition among the elderly focused on perceptual and attentional processing, while only a few examined mnemonic processing. Nevertheless, working memory processing is also an important aspect of emotional cognition, which is suggested as a core cognitive ability (Jackson et al., 2008, 2009; Jackson et al., 2014; Thomas et al., 2014; Stiernströmer et al., 2016). The capacity of the central executive system in working memory declined with age (Baddeley, 1986), resulting in a lower information-processing capacity among the elderly (Salthouse, 2016). Some studies indicated that emotion enhanced the working memory among both younger and elder adults, regardless of the valence of emotion (Mammarella et al., 2013; Truong and Yang, 2014). However, other studies suggested a positivity superiority in the processing of working memory among the elderly (Mikels et al., 2005; Bermudez and Souza, 2017). Therefore, the effect of emotion on working memory processing of faces among widowed elderly remains to be examined.

Taken together, this study was designed to reveal the emotional cognitive deficits among widowed elderly, by comparing attentional bias and mnemonic bias to emotional stimuli between widowed and non-widowed elderly. Furthermore, we aimed to examine the role of the negative emotional state induced by widowhood in the cognitive deficits among widowed individuals.

The results of this study may help test and develop existing theories such as the socioemotional selectivity theory and the cognitive-behavioral model and help develop interventions on the emotional problems among widowed elderly.

MATERIALS AND METHODS

Participants

Forty-four widowed elderly (i.e., 29 women, WE group) and 44 non-widowed elderly (i.e., 22 couples, NWE group) were recruited from southwestern China. The inclusion criteria for the WE group were: (1) older than 55 years; (2) currently widowed and has no partner; and (3) able to understand the contents of the questionnaires and to complete the behavioral tasks. The inclusion criteria for the NWE group were: (1) older than 55 years; (2) currently in marriage and lives with the partner; and (3) the couple could both understand the contents of the questionnaires and complete the behavioral tasks. All of the participants were right-handed and had normal or corrected-to-normal vision and normal color vision. We performed a power analysis to determine the sample size using the G*Power 3.1.9.7 software (Faul et al., 2009). To find a significantly different effect between groups, we set the level of effect size as $d = 0.8$ with a statistical power of 0.9. The result showed that two samples of 34 subjects, at least, were required. The distribution of sex was not significantly different between groups ($\chi^2 = 2.28$, $p = 0.131$). However, the age of the WE group ($M = 70.68$, $SD = 7.35$, range: 59–87 years old) was significantly larger than that of the NWE group ($M = 65.86$, $SD = 5.69$, range: 55–77 years old) [$t(86) = 3.44$, $p = 0.001$]. Therefore, age was treated as a covariate in all the analyses. In addition, although the sex distribution was not significantly different between groups, to fully exclude the influence of sex, we also treated sex as a covariate in all the analyses. The study was approved by the ethics committee for human research at Zunyi Medical University, and informed consent was obtained from all participants.

Measurements

All the participants completed two scales before they participated in behavioral experiments.

The Geriatric Depression Scale (GDS; Yesavage et al., 1982). The Geriatric Depression Scale (GDS) is designed to measure depression in the elderly (Yesavage, 1988) and has been widely used among the elderly (Durmaz et al., 2018; Shin et al., 2019; Krishnamoorthy et al., 2020). It consists of 30 items, and participants respond to the items by choosing *yes* or *no*. The total score ranges from 0 to 30 and indicates the severity of depression.

The State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). The State-Trait Anxiety Inventory (STAI) can differentiate between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety" (Spielberger et al., 1983; Spielberger, 2010). In this study, we focused on the impact of spousal bereavement on the mental health of the elderly. Therefore, state anxiety may be more related to our purpose, and the influence of trait anxiety should be excluded. The scale consists of two subscales, namely, STAI-S and STAI-T. The STAI-S subscale consists of twenty items, which assess the state anxiety. The STAI-T subscale also consists of twenty items, which assess the general anxiety as a long-standing trait. The total scores of the two subscales both range from 20 to 80 and indicate the severity of anxiety.

Experiment 1: The Visual Search Task

Stimuli

Sixteen sad faces, sixteen angry faces, and sixteen happy faces were selected from the Chinese Facial Affective Picture System (CFAPS) as search targets. Fifty-eight neutral faces selected from the CFAPS were treated as distractors. Half of the faces were women, and the other half were men. The hair, ears, and necks of all faces were removed using the Photoshop software. We then laid each picture on a black background and cropped it into a uniform size (130 × 150 pixels). All photos were then grayscaled and matched for brightness and contrast using the MATLAB software. The valence and arousal of each face were evaluated on 9-point scales. Valence was significantly different among three categories of emotional faces [$F(2, 30) = 351.92$, $p < 0.001$, $\eta_p^2 = 0.959$]. *Post-hoc* tests with Bonferroni adjustment revealed that the valence of happy faces ($M = 6.74$, $SD = 0.51$) was higher than that of sad faces ($M = 2.84$, $SD = 0.54$) and angry faces ($M = 2.62$, $SD = 0.40$) (all $p < 0.001$), while the valence was not different between sad and angry faces ($p = 0.760$). The difference of arousal among the three categories of emotional faces was non-significant [$F(2, 30) = 1.59$, $p = 0.224$,$\eta_p^2 = 0.096$].

Procedure

The visual stimuli were presented on a SAMSUNG 19-in LCD screen (spatial resolution: 1,280 × 800; refresh rate: 60 Hz), with a Dell PC (CPU: Intel Core i5-4590; Graphics card: Intel HD Graphics 4600; RAM: 4 GB) (Zhang et al., 2018). The subjects viewed the stimuli from a distance of 60 cm. The presentation of stimuli was controlled using the E-Prime 2.0 software.[1]

In a visual search task, participants are asked to find a target among several distractors. In this study, the target was the emotional face (i.e., with happy, sad, or angry expression), while the distractor was the neutral face. At the beginning of each trial, a white fixation cross was presented at the center of the black screen for a random period of 500–1,500 ms. Then, an array of eight faces or two faces appeared until a response was made. In 75% of the trials, the array contained a search target, while in the rest trials, the target was absent. Participants were asked to press one key (F) if they found the target (an emotional face) among the distractors (neutral faces) and another key (J) if the target was absent as quickly and accurately as possible. The next trial began after a blank screen for 500 ms. Each experimental block consisted of 64 trials. The set size (i.e., number of faces in the face array) and search target were fixed in each block. As there were two kinds of set size (two or eight faces) and three kinds of search targets (i.e., sad, angry, or happy faces), each participant was required to complete six experimental blocks of 384 trials. The location of the target and the identity of faces were randomized trial by trial.

[1] https://www.pstnet.com

Designs and Analysis

This experiment was a 3 (emotional type: sad/angry/happy) × 2 (set size: 2/8) × 2 (group: WE/NWE) mixed design, with the emotional type and set size as within-subject factors and the group as a between-subject factor. As discussed in participants, age and sex were treated as covariates in all the analyses.

First, accuracies were calculated and analyzed with a 3 (emotional type) × 2 (set size) × 2 (group) mixed analysis of covariance (ANCOVA). Second, RTs beyond 3 SD from the mean RT were excluded. RTs were then calculated based on remaining trials and analyzed with a 3 (emotional type) × 2 (set size) × 2 (group) mixed ANCOVA. Third, for the visual search paradigm, the search slope is an indicator of search efficiency. The search slope is defined as the slope of the fitted line of RT against set size. In this study, the search slope = (RT_8–RT_2)/(8–2). RT_8 denotes the RT from trials with eight faces, while RT_2 denotes the RT from trials with two faces. The larger the slope, the lower the efficiency of searching the targets. Search slopes were analyzed with a 3 (emotional type) × 2 (group) mixed ANCOVA.

Experiment 2: The Delayed-Match-to-Sample Task

Stimuli

Seventy-two emotional faces, namely, 24 sad, 24 angry, and 24 happy faces, were selected from CFAPS, half of which were female faces. Images were processed in the same way as Experiment 1, except that the image size was set to 185 × 200 pixels. Repeated measures ANOVA showed that the valences were different among emotional faces [$F(2, 46) = 632.01$, $p < 0.001$,$\eta_p^2 = 0.965$]. *Post-hoc* tests suggested that the valence of happy faces ($M = 6.54$, $SD = 0.64$) was significantly higher than those of angry ($M = 2.70$, $SD = 0.44$) and sad ($M = 2.85$, $SD = 0.48$) faces ($ps < 0.001$), while the difference was not significant between sad and angry faces ($p = 0.490$). In addition, no significant difference in arousal was found [$F(2, 46) = 2.67$, $p = 0.080$, $\eta_p^2 = 0.104$].

Procedure

In a DMTS task, participants were asked to briefly remember a sample stimulus for a few seconds. Then, a test stimulus was presented, and participants compared it with the sample stimulus. In this study, each trial began with a white cross at the center of the black screen for a random period of 500–1,500 ms. Subsequently, two faces (sample) with the same expression appeared for 1,000 ms at two of the four-quadrant of the visual field. Afterward, a blank screen was presented for 2,000 ms, and participants were asked to maintain the two faces they just saw in their minds. Then, a test face was presented at the center of the screen for 1,000 ms. The test face matched the sample face in half of the trials. Subjects were asked to determine whether the test face matched one of the two sample faces (F for yes, J for no). The next trial began after a response was made. Each block included 48 trials and contained faces with one facial emotion. As there were three kinds of emotions, each participant was required to complete three blocks in the experiment. The sequence of blocks was randomized among participants.

Designs and Analysis

This experiment was a 3 (emotional type: sad/angry/happy) × 2 (group: WE/NWE) mixed design, with the emotional type as a within-subject factor and group as a between-subject factor. Age and sex were treated as covariates in all the analyses.

First, accuracies were calculated and analyzed with a 3 (emotional type) × 2 (group) mixed ANCOVA. Second, RTs within the 3 SD from the mean RT were calculated and analyzed with a 3 (emotional type) × 2 (group) mixed ANCOVA. Third, we calculated the discriminability index, d', according to the signal detection theory. d' is defined as the distance between the two distributions of signal and noise. In this study, a signal is a face that matched the sample face, while noise is a face that did not match any sample faces. The hit rate and false alarm rate were calculated first. d' was then calculated as Z(Hit)-Z(False alarm). Z is the Z-transformed score of a rate. A larger d' denotes a higher discriminability of the subject in identifying matched or unmatched faces.

Modeling Analysis

To investigate the moderation effects of depression and anxiety on the relationship between widowhood and cognitive processing, we performed the modeling analysis using the PROCESS V3.4.1 plugin in the SPSS 23.0 software.[2] Moderation models were constructed whenever the between-group difference of cognitive processing was found. In these models, the group was set as the independent variable (0 = NWE, 1 = WE); behavioral performance was set as the dependent variable (e.g., RT in searching sad face among eight items); the GDS score or STAI-S score was set as the moderator; age and sex were set as covariates.

RESULTS

The Level of Depression and Anxiety

The demographics and scale scores are summarized in **Table 1**. The WE group showed a higher depression level and a higher state anxiety level than the NWE group (both $p < 0.05$), while the trait anxiety was not significantly different between the two groups ($p = 0.560$).

[2]www.ibm.com/analytics/spss-statistics-software

TABLE 1 | Demographics and scale scores [mean (SD)].

	WE ($N = 44$)	NWE ($N = 44$)	t/χ^2	p
Age (years)	70.68 (7.35)	65.86 (5.70)	3.44	0.001
Sex (female/male)	29/15	22/22	2.29	0.131
GDS	10.23 (5.87)	7.91 (4.03)	2.16	0.034
STAI-S	36.82 (8.19)	32.89 (5.86)	2.59	0.011
STAI-T	38.84 (7.34)	37.93 (7.17)	0.58	0.560

WE, widowed elderly; NWE, non-widowed elderly; GDS, Geriatric Depression Scale; STAI-S, State-Trait Anxiety Inventory–State anxiety subscale; STAI-T, State-Trait Anxiety Inventory–Trait anxiety subscale.

Experiment 1: The Visual Search Task

Averaged accuracies, RTs, and slopes are presented in **Supplementary Table 1**.

First, a 3 (emotional type) × 2 (set size) × 2 (group) mixed ANCOVA was performed on the accuracies. No significant interactions and main effects were found (all $F < 1.9$, $p > 0.1$, $\eta_p^2 < 0.03$).

Next, the same 3 × 2 × 2 mixed ANCOVA was performed on the RTs. There was a significant interaction between the set size and group[($F(1, 84) = 10.99$, $p = 0.001$, $\eta_p^2 = 0.116$]. The simple effect analysis showed that WE responded more slowly than NWE when the set size was 8 ($p = 0.003$), while the difference was non-significant when the set size was 2 ($p = 0.406$). Furthermore, the interaction between the emotional type and set size was significant [$F(2, 168) = 3.27$, $p = 0.041$, $\eta_p^2 = 0.037$]. The simple effect analysis showed that the effect of the emotional type was marginally significant when the set size was 8 ($p = 0.092$), while it was non-significant when the set size was 2 ($p = 0.800$). Specifically, when the set size was 8, RTs to happy faces were faster than those to sad ($p < 0.001$) and angry ($p < 0.001$) faces. In addition, there were significant main effects of set size [$F(1, 84) = 10.87$, $p = 0.001$, $\eta_p^2 = 0.115$] and group [$F(1, 84) = 5.04$, $p = 0.027$, $\eta_p^2 = 0.057$], indicating faster responses at set size of 2 and in the NWE group. Other interactions and main effects were non-significant (all $F < 2.3$, $p > 0.1$, $\eta_p^2 < 0.03$).

Finally, a 3 (emotional type) × 2 (group) mixed ANCOVA was performed on the search slopes. We found a significant main effect of group [$F(1, 84) = 10.99$, $p = 0.001$, $\eta_p^2 = 0.116$], indicating lower search efficiencies among WE. Furthermore, the main effect of the emotional type was significant [$F(2, 168) = 3.27$, $p = 0.041$, $\eta_p^2 = 0.037$]. *Post-hoc* tests showed a marginally significant difference between the slopes for happy and sad faces ($p = 0.093$). The interaction between the emotional type and the group was non-significant [$F(2, 168) = 1.53$, $p = 0.219$, $\eta_p^2 = 0.018$].

Experiment 2: The Delayed-Match-to-Sample Task

We first performed a 3 (emotional type) × 2 (group) mixed ANCOVA on the accuracies. Results showed that the interaction effect was significant [$F(2, 168) = 3.69$, $p = 0.027$, $\eta_p^2 = 0.042$]. The simple effect analysis revealed that WE had lower accuracies in memorizing sad ($p = 0.071$) and angry ($p = 0.050$) faces than NWE, while the difference was non-significant for happy faces ($p = 0.559$). The main effects of emotional type and the group were non-significant (both $F < 2.2$, $p > 0.1$, $\eta_p^2 < 0.03$).

Next, a 3 (emotional type) × 2 (group) mixed ANCOVA was performed on the RTs. No significant interaction and main effects were found (all $F < 1.6$, $p > 0.2$, $\eta_p^2 < 0.02$).

Finally, a 3 (emotional type) × 2 (group) mixed ANCOVA on the d'. Similar to the accuracy results, we found a significant interaction effect between the emotional type and group [$F(2, 168) = 4.12$, $p = 0.018$, $\eta_p^2 = 0.047$]. The simple effect analysis revealed lower discriminability among WE in memorizing sad ($p = 0.071$) and angry ($p = 0.037$) faces than NWE, while the difference was non-significant for happy faces ($p = 0.544$). The main effects of the emotional type and the group were non-significant (both $F < 1.6$, $p > 0.2$,$\eta_p^2 < 0.02$).

Modeling Analysis

First, regarding the visual search task, we found significant between-group differences on the RTs at a set size of 8, as well as the difference on the search slopes. Therefore, six moderation models with depression as moderators and six moderation models with state anxiety as moderators were constructed. As we described in methods, group and behavioral performance were set as the independent variable and dependent variable, respectively. The level of depression or state anxiety was set as the moderator. Age and sex were set as the covariates. The moderation effects of depression and state anxiety are summarized in **Tables 2**, **3**, respectively. The results only showed a significant moderation effect of state anxiety in the relationship between the group and RTs for happy faces (**Table 3**). Simple slope tests (**Figure 1**) revealed that NWE showed faster responses to happy faces than WE only among high state anxiety individuals ($b = 1{,}605.76$, $t = 3.51$, $p = 0.001$, 95%CI [696.30, 2,515.21]), while the difference was non-significant among low state anxiety individuals ($b = 326.73$, $t = 0.75$, $p = 0.453$, 95%CI [–536.63, 1,190.09]).

Next, regarding the DMTS task, we found significant between-group differences in the accuracies and d' for sad and angry faces. Therefore, four moderation models with depression as moderators and four moderation models with state anxiety as moderators were constructed. Results are summarized in **Tables 4**, **5**. All the moderation effects were significant. The simple slope analysis (**Figure 2**) on the effect of depression revealed that NWE showed a higher mnemonic accuracy

TABLE 2 | The interaction effects of group × depression in the visual search task.

Dependent variables	*b*	*SE*	*t*	*p*	95%CI
Search slope (sadness)	−4.94	11.09	−0.45	0.66	[–27.01, 17.13]
Search slope (anger)	−13.54	9.66	−1.40	0.16	[–32.76, 5.67]
Search slope (happiness)	12.67	10.31	1.23	0.22	[–7.85, 33.18]
RT at set size of 8 (sadness)	18.95	76.06	0.25	0.80	[–132.35, 170.25]
RT at set size of 8 (anger)	7.36	71.07	0.10	0.92	[–134.02, 148.75]
RT at set size of 8 (happiness)	114.24	61.02	1.87	0.06	[–7.15, 235.62]

TABLE 3 | The interaction effects of group × state anxiety in the visual search task.

Dependent variables	*b*	*SE*	*t*	*p*	95%CI
Search slope (sadness)	5.22	7.79	0.67	0.50	[–10.28, 20.71]
Search slope (anger)	−8.28	6.83	−1.21	0.23	[–21.87, 5.32]
Search slope (happiness)	7.58	7.29	1.04	0.30	[–6.91, 22.08]
RT at set size of 8 (sadness)	89.12	52.50	1.70	0.09	[–15.32, 193.56]
RT at set size of 8 (anger)	46.74	49.47	0.94	0.35	[–51.67, 145.15]
RT at set size of 8 (happiness)	87.04	42.97	2.03	**0.04**	[1.56, 172.51]

Bold values denote significant statistical results with p values < 0.05.

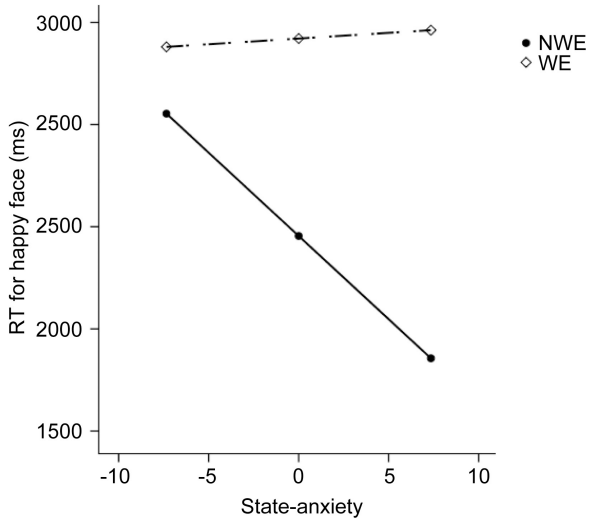

FIGURE 1 | The moderation effect of state anxiety on the relationship between widowhood and the performance in the visual search experiment. The dependent variable here is the reaction time (RT) for happy faces at the set size of 8. NWE, non-widowed elderly; WE, widowed elderly.

TABLE 4 | The interaction effects of group × depression in the DMTS task.

Dependent variables	*b*	*SE*	*t*	*p*	95%CI
Accuracies (sadness)	−0.01	0.004	−2.88	**0.01**	[−0.02, −0.004]
Accuracies (anger)	−0.01	0.01	−2.54	**0.01**	[−0.02, −0.002]
d′ (sadness)	−0.08	0.03	−2.72	**0.01**	[−0.14, −0.02]
d′ (anger)	−0.07	0.03	−2.60	**0.01**	[−0.13, −0.02]

Bold values denote significant statistical results with p values < 0.05.

TABLE 5 | The interaction effects of group × state anxiety in the delayed-match-to-sample (DMTS) task.

Dependent variables	*b*	*SE*	*t*	*p*	95%CI
Accuracies (sadness)	−0.01	0.003	−2.02	**0.04**	[−0.01, −0.0001]
Accuracies (anger)	−0.01	0.004	−2.74	**0.01**	[−0.02, −0.003]
d′ (sadness)	−0.05	0.02	−2.20	**0.03**	[−0.09, −0.01]
d′ (anger)	−0.06	0.02	−2.83	**0.01**	[−0.10, −0.02]

Bold values denote significant statistical results with p values < 0.05.

and discriminability than WE only among high-depressive individuals (accuracies for sad faces: $b = -0.12$, $t = -3.40$, $p = 0.001$, 95%CI [−0.19, −0.05]; accuracies for angry faces: $b = -0.12$, $t = -3.25$, $p = 0.002$, 95%CI [−0.20, −0.05]; d' for sad faces: $b = -0.74$, $t = -3.25$, $p = 0.002$, 95%CI [−1.19, −0.29]; d' for angry faces: $b = -0.74$, $t = -3.39$, $p = 0.001$, 95%CI [−1.18, −0.31]) but not among low-depressive individuals. Similar results were found on the effect of state anxiety (**Figure 3**). NWE showed a higher mnemonic accuracy and discriminability than WE only among high state anxiety individuals (accuracies for sad faces: $b = -0.10$, $t = -2.70$, $p = 0.008$, 95%CI [−0.17, −0.03]; accuracies for angry faces: $b = -0.74$, $t = -3.61$, $p = 0.001$, 95%CI [−0.21, −0.06]; d' for sad faces: $b = -0.65$, $t = -2.85$, $p = 0.006$, 95%CI [−1.10, −0.20]; d' for angry faces: $b = -0.80$, $t = -3.78$, $p < 0.001$, 95%CI [−1.21, −0.38]) but not among low state anxiety individuals.

DISCUSSION

In this study, we examined the effect of spousal bereavement on the emotional state and emotional cognition among the elderly. First, we found that WE indeed showed a higher level of depression and state anxiety than NWE, consistent with previous studies (Williams, 2005; Ward et al., 2007; Sikorski et al., 2014; Tseng et al., 2017; Verma et al., 2019). Second, accompanied by these emotional problems, emotional cognitions were impaired. Specifically, a general deficit in visual search efficiency was observed among WE. However, the deficits in visual working memory were restricted to negative emotions (i.e., sadness and anger). We further examined the moderating effects of emotional problems on the relationship between spousal bereavement and emotional cognition deficits. The results mainly showed that emotional problems could modulate the effect of spousal bereavement on working memory deficits, i.e., the deficits were only evident among individuals with a high level of emotional problems. These results demonstrated different mechanisms between the deficits in attentional processing and mnemonic processing among WE.

In general, our results revealed cognitive deficits among WE, consistent with previous findings (S.H. Shin et al., 2018). After controlling for the effects of depression, social vulnerability, and stress, widowhood still showed a negative influence on the cognitive health of elderly (Zhao et al., 2021). The core of cognitive abilities is mainly limited by information-processing capacity, which decreases with age (Lavie, 2005; Salthouse, 2016). Previous studies suggested that widowed elderly people showed declined information-processing speed (Ward et al., 2007; Atalay and Staneva, 2020). Our results also suggest that WE had declined information-processing capacity. For example, when the task requirement was relatively low (e.g., only one distractor in the visual search task), WE performed equally well as NWE.

Although the general deficit was found on emotional cognition, the effects of the emotional valance on these deficits may be different between specific tasks. For the attentional processing, the deficits seemed not dependent on the emotional valence. It seemed to support neither the socioemotional selectivity theory nor the cognitive-behavioral model. According to the socioemotional selectivity theory (Carstensen et al., 1999), all elderly should have attentional biases toward happy faces. And according to the cognitive-behavioral model (Beck, 1964, 1967; Rapee and Heimberg, 1997; Turk et al., 2001; Heimberg et al., 2010; Beck and Haigh, 2014), the WE should have attentional biases toward sad faces with their increasing level of anxiety and depression. A potential reason may be that the deficits in attentional processing might stem from inhibitory deficits. According to the inhibitory deficit theory of cognitive aging, the ability to inhibit irrelevant information in selective attention declines with age (Hasher and Zacks, 1988). Studies found that stressful and traumatic experiences impaired inhibitory control (Covey et al., 2013; Roos et al., 2017; Herd et al., 2018;

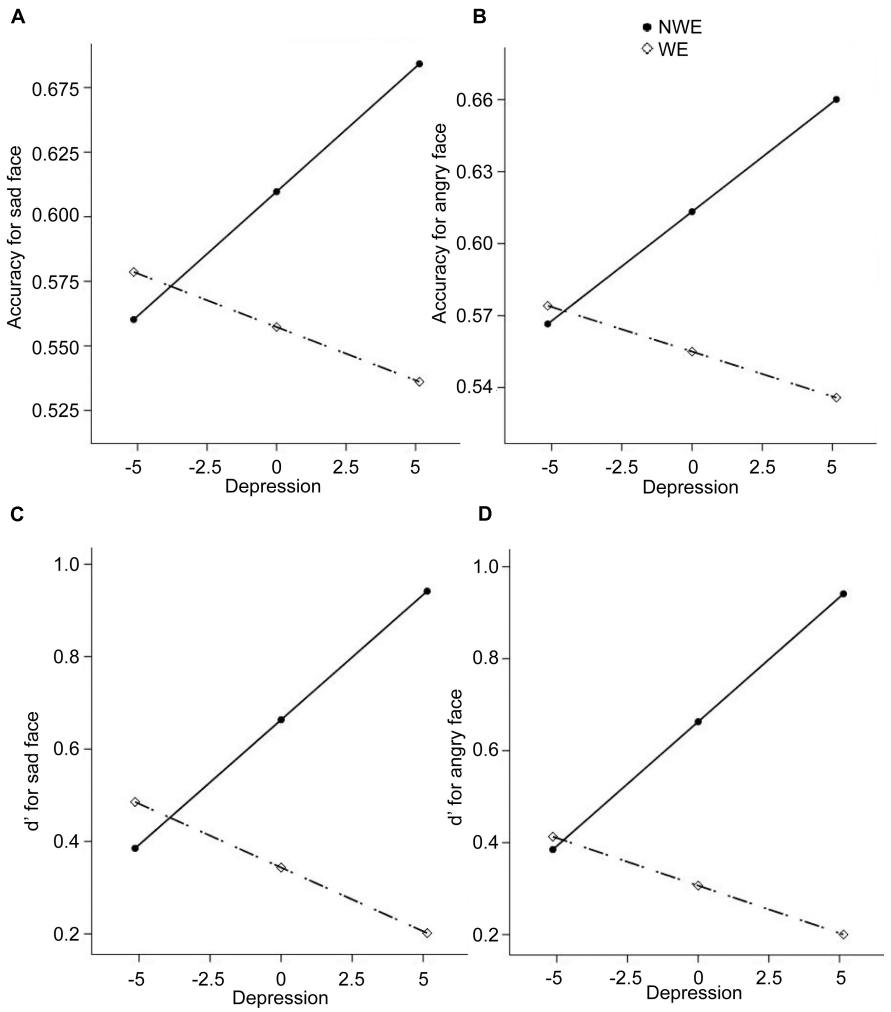

FIGURE 2 | The moderation effect of depression on the relationship between widowhood and the performance in the delayed-match-to-sample (DMTS) experiment. The dependent variables are the mnemonic accuracy for sad faces, the mnemonic accuracy for angry faces, *d′* for sad faces, and *d′* for angry faces, respectively, for **(A–D)**. NWE, non-widowed elderly; WE, widowed elderly.

Melara et al., 2018). Therefore, WE may have more difficulty in suppressing distractors and exhibit a lower search efficiency than NWE. For the mnemonic processing, WE showed lower accuracies and discriminability in memorizing sad and angry faces but not happy faces compared with NWE, suggesting that the deficits in working memory were restricted to negative emotions. More detailed, such deficits were evident only when the depression/state anxiety levels of individuals were high. From the simple slope analysis, we may find that the mnemonic processing increased with the level of emotional problems among NWE, which was the main reason for the moderation effects. Such a pattern of performance could be explained by the cognitive-behavioral model that the WE with high anxiety/depression have distorted or dysfunctional schemas that can distort information processing and thus were more likely to have biased working memory to sad and angry faces. A lot of studies demonstrated that depressed individuals exhibited deficits in removing/inhibiting negative stimuli (e.g., negative words) from working memory (Joormann, 2004; Joormann and Gotlib, 2008; Yoon et al., 2014) and had difficulties in disengaging sad faces from working memory (Levens and Gotlib, 2010; Foland-Ross et al., 2013), resulting in higher accuracy in working memory for negative pictures (Linden et al., 2011; Li et al., 2018). A functional MRI (fMRI) study with the *n*-back task showed greater activations elicited by negative emotional stimuli in left DLPFC among patients with depression (Kerestes et al., 2012). Therefore, the better performance of NWE on the memory for sad and angry faces may primarily result from their depression or state anxiety.

However, the working memory for negative faces among WE was less affected by their emotional problems compared with NWE, which was inconsistent with the cognitive-behavioral model. This result may stem from the impairment of working memory among WE. First, widowhood might impair working memory. Studies revealed that spousal bereavement was associated with declines in working memory among the elderly (Atalay and Staneva, 2020; Zhao et al., 2021). Second, emotional

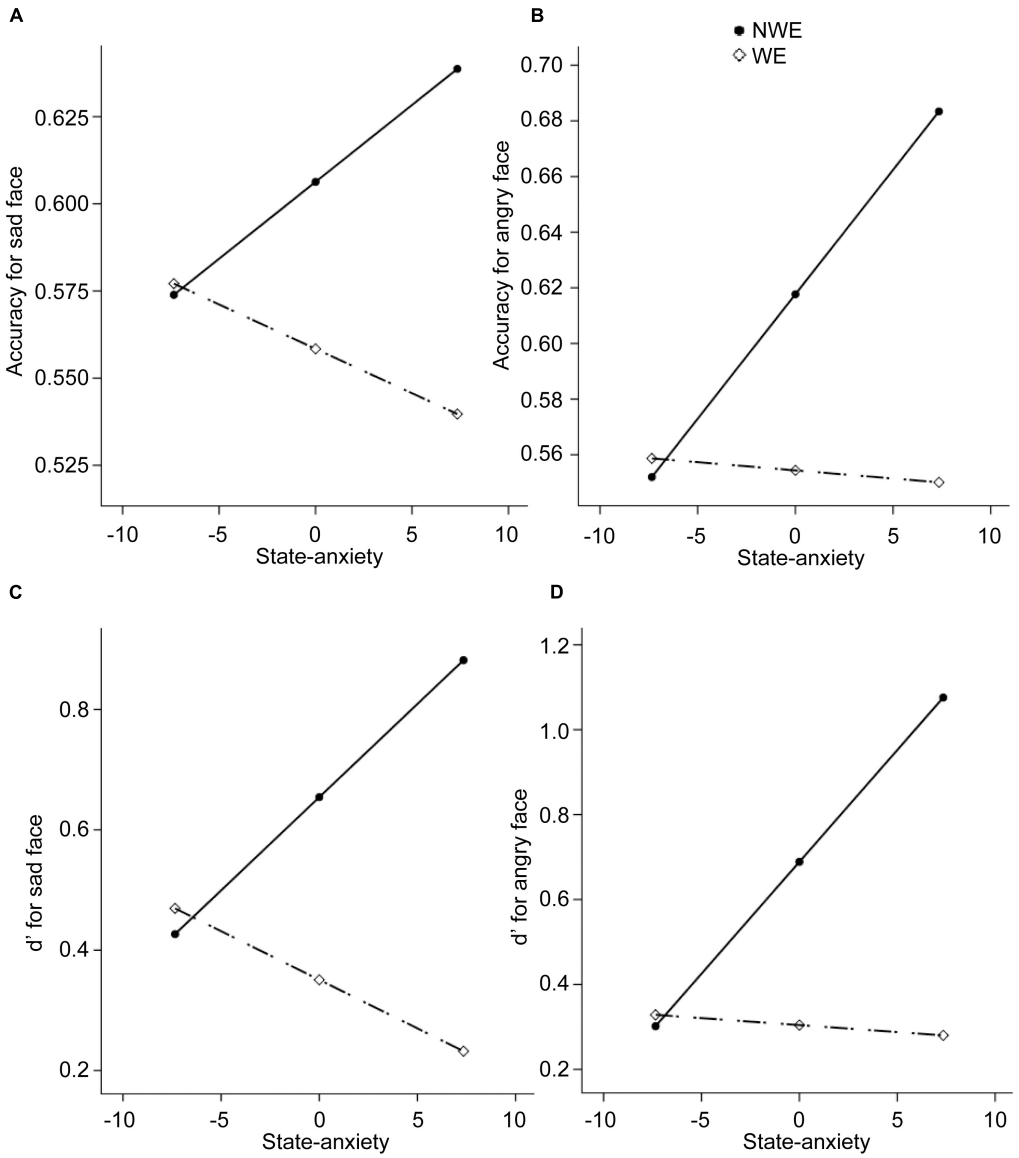

FIGURE 3 | The moderation effect of state anxiety on the relationship between widowhood and the performance in the DMTS experiment. The dependent variables are the mnemonic accuracy for sad faces, the mnemonic accuracy for angry faces, *d′* for sad faces, and *d′* for angry faces, respectively, for **(A–D)**. NWE, non-widowed elderly; WE, widowed elderly.

problems might also impair working memory. Previous studies revealed that individuals with a negative emotional state (e.g., depression and anxiety) performed poorly on working memory (Nebes et al., 2000; Lavric et al., 2003; Harvey et al., 2004; Christopher and MacDonald, 2005; Rose and Ebmeier, 2006; Shackman et al., 2006; Spachtholz et al., 2014; Moran, 2016; Guo et al., 2020), while positive mood could enhance working memory capacity (Storbeck and Maswood, 2016). Electrophysiological evidence further indicated that the negative emotional state led to reduced P3b amplitude at the encoding and retrieval phases of working memory (Li et al., 2010). Taken together, the working memory is dysfunctional among WE and may not be sensitive anymore to emotional problems.

Limitations

Although the effects of age and sex were controlled statistically in this study, we still know less about the impact of age and sex on our results. First, studies with stricter control are required. Second, as there was evidence showing moderation effects of sex and age on the impact of spousal bereavement on memory (Rosnick et al., 2010), the interaction effects of age, sex, and spousal bereavement among the elderly should be further examined.

Besides, the faces adopted in this study were mainly the faces of young adults. A previous study found that the elderly showed attentional bias to own-age face cues regardless of the emotional valence, which was similar to our results

(Noh and Isaacowitz, 2011). However, whether the properties of faces could affect cognitive processing remains to be investigated.

CONCLUSION

Widowed elderly had a general deficit in search efficiency across emotional types, while they showed mnemonic deficits in negative faces but not positive faces. Furthermore, the level of depression or state anxiety of the elderly moderated the effects of widowhood on the deficits of mnemonic processing, i.e., the deficits were only evident among WE with a high level of depression or state anxiety. These findings reveal the attentional deficits in sad, angry, and happy faces, and the mnemonic deficits in sad and angry faces among elderly who suffer from widowhood, and point out the important role of emotional problems such as depression and state anxiety in modulating these emotional cognitive deficits.

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 human participants were reviewed and approved by the Ethics Committee for Human Research at Zunyi Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TB: conception, design, acquisition of data, analysis of data, interpretation of data, funding acquisition, writing–original draft, and writing—review and editing. HK: conception, design, data acquisition, data analysis, data interpretation, funding acquisition, and writing—review and editing. YK: conception, design, acquisition of data, and writing—review and editing. BS: conception, design, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.808885/full#supplementary-material

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Auditory Cognitive Training Improves Brain Plasticity in Healthy Older Adults: Evidence From a Randomized Controlled Trial

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The number of older adults is increasing globally. Aging is associated with cognitive and sensory decline. Additionally, declined auditory performance and cognitive function affect the quality of life of older adults. Therefore, it is important to develop an intervention method to improve both auditory and cognitive performances. The current study aimed to investigate the beneficial effects of auditory and cognitive training on auditory ability and cognitive functions in healthy older adults. Fifty healthy older adults were randomly divided into four training groups—an auditory-cognitive training group (AC training; n = 13), an auditory training group (A training; n = 13), a cognitive training group (C training; n = 14), and an active control group (n = 12). During the training period, we reduced the sound intensity level in AC and A training groups and increase training task difficulty in AC, A, and C training groups based on participants' performance. Cognitive function measures [digit-cancelation test (D-CAT); logical memory (LM); digit span (DS)], auditory measures [pure-tone audiometry (PTA)], and magnetic resonance imaging (MRI) scans were performed before and after the training periods. We found three key findings. First, the AC training group showed difference between other training groups (A, C, and active control training groups) in regional gray matter volume (rGMV) in the right dorsolateral prefrontal cortex, the left inferior temporal gyrus (L. ITG), the left superior frontal gyrus, the left orbitofrontal cortex, the right cerebellum (lobule 7 Crus 1). Second, the auditory training factor groups (ATFGs, the AC and A training groups) improved auditory measures and increased the rGMV and functional connectivity (FC) in the left temporal pole compared to the non-ATFGs (the C training group and active control group). Third, the cognitive training factor groups (CTFGs; the AC and C training groups) showed statistically significant improvement in cognitive performances in LM and D-CAT compared to the non-CTFGs (the A training group and active control group). Therefore, the auditory training factor and cognitive training factor would be useful in enhancing the quality of life of older adults. The current AC training study, the plasticity of the brain structure was observed after 4 weeks of training.

Keywords: auditory-cognitive training, cognitive function, auditory ability, older adults, temporal pole

INTRODUCTION

Aging is associated with cognitive and sensory decline (Deal et al., 2017). The incidence of age-related hearing loss (ARHL) has been increasing among older adults worldwide. Hearing loss has become a public health problem with the burgeoning aging population (WHO, 2011). ARHL is characterized by degeneration of the mechanotransducing inner and outer hair cells of the cochlea as well as the auditory nerve (neural presbycusis) (Schuknecht and Gacek, 1993; Ohlemiller, 2004). In addition to peripheral lesions, changes are likely to occur in the central auditory pathways, and these contribute to the development and progression of ARHL (Jayakody et al., 2018). ARHL is a multifactorial disorder with several underlying risk factors, such as age, environment, and lifestyle (Yamasoba et al., 2013). ARHL causes speech perception problems (Lin, 2011) and has been linked to consequent decline in cognitive function (Deal et al., 2017; Kawata et al., 2021), increased social isolation (Mick et al., 2014), reduced quality of life (Li et al., 2014), increased risk of depression (Li et al., 2014), and decline in ability to independently perform activities of daily living (Dalton et al., 2003). Epidemiological evidence across populations suggests that cognitive decline with ARHL is a risk factor for the development of dementia in older adults (Taljaard et al., 2016).

Speech comprehension involves the perceptual sensitivity of the peripheral nervous system and the language-specific cognitive abilities of the central nervous system (Sommers, 1997). Success in achieving listening goals may depend on the distribution of greater cognitive functions of the listeners and the quality of the signals (Pichora-Fuller et al., 2016). Therefore, it is important to consider the aspects of both hearing and cognitive functions. Multiple factors (such as hearing loss and decline in cognitive function) contribute to speech recognition difficulties (Wayne and Johnsrude, 2015; Kawata et al., 2020). When a speech signal is poorly processed, it is transmitted from the ear to the brain, and greater cognitive resources may be required to interpret the meaning of the sound than would be with a properly processed sound (Schneider et al., 2010). Thus, there is no guarantee that increasing cognitive energy will solve hearing problems. Therefore, success in achieving auditory goals may depend on the considerable cognitive energy expenditure that is required when the quality of the signal available to the listener is suboptimal. Therefore, it would be important to improve cognitive function as well as auditory sensory function. One approach is using a combination of auditory and cognitive training (AC training). Recently, an AC training has been proposed (Yusof et al., 2019). Yusof used AC training to improve speech recognition, auditory processing, and cognitive abilities in older adults with normal cognitive and mild cognitive impairment (Yusof et al., 2019). Yusof used five adaptive training tasks (word-in-noise, sentence-in-noise, word span, word order, and word position). After 8 weeks' of AC training, improvements in general cognitive functions measured by Montreal Cognitive Assessment and auditory processing ability measured by a dichotic digits test was observed in older adults with normal cognition and neurocognitive impairment compared to that of a control group.

A previous study reported that AC training had positive effects on cognitive and auditory functions (Yusof et al., 2019). However, some limitations were noted. First, they did not directly measure auditory abilities using objective auditory assessment measures, such as the pure-tone audiometry (PTA) threshold. Second, they did not use a suitable active control group. In the previous study, the control group participants were asked to watch documentary programs on history and literature using the same device used for AC training (Yusof et al., 2019). This ensured that the control and training groups matched in terms of training duration and the auditory stimuli received. However, it is unclear which components of the auditory and cognitive aspects are important for improving cognitive and auditory performance. Third, the previous study used different signal-to-noise-ratio to modify the difficulty of the task (Yusof et al., 2019). Although it is important to listen to the words and sentences with noises (Pichora-Fuller et al., 1995), older adults usually show difficulty with low sound intensity level [decibel (dB)] (Slade et al., 2020). Fourth, previous study did not investigate whether AC training affect neural systems. It is still unclear that AC training would have positive effects on brain functions and brain structures.

The present study was designed to evaluate the beneficial effects of AC training on hearing ability and cognitive and brain functions in healthy older adults. We conducted a single-blinded randomized controlled trial using an AC training group, an auditory (A) training group, a cognitive (C) training group, and an active control group. Considering the abovementioned shortcomings of the previous studies, we used objective auditory measures (PTA) to assess auditory abilities. Moreover, to resolve the issue with the active control group, we used an active control group that eliminated the need for change in cognitive or auditory training difficulty. In this study, we controlled the sound intensity level to manipulate the auditory factor during training. By controlling the sound intensity level, we were able to control auditory training factor in the AC and A training groups. Furthermore, we conducted magnetic resonance imaging (MRI) before and after training to investigate changes in brain plasticity after training. In the field of cognitive aging, the application of structural and functional connectivity of the brain is particularly important because these brain changes usually precede behavioral changes (Farras-Permanyer et al., 2019). In addition, previous studies demonstrated that cognitive training led to change brain structures (gray matter volume) and functional connectivity after interventions (Chaddock-Heyman et al., 2021; Yin et al., 2021). Based on the previous finding, we investigated brain plasticity using MRI with change in the regional gray matter volume and the resting-state functional connectivity.

The present study conducted a training period of 4 weeks. Previous studies of auditory training performed auditory training for 4 weeks (Karawani et al., 2016). Significant improvements were observed in all training conditions in both the ARHL and normal hearing groups. Improvements in assessments of cognitive function after 4 weeks of training have been reported in a study of cognitive training in the elderly (Biel et al., 2020). Moreover, the previous AC training study conducted training for 8 weeks (Yusof et al., 2019). The participants were evaluated after 4 and 8 weeks of training. Both the normal hearing and hearing

loss groups were shown to have improved auditory processing and cognitive function. In a cognitive training study, the plasticity of the brain structure was observed after 4 weeks of training (Biel et al., 2020). For this reason, the present study conducted training for 4 weeks.

This is the first study to use AC training with a lower intensity level than the subjective comfortable listening level to control the difficulty in auditory training factor. To evaluate the beneficial effect of AC training on auditory ability and cognitive and brain functions in healthy older adults, we used PTA to measure auditory performance, cognitive measures (D-CAT, LM, DS), and brain structure and functional connectivity (FC).

We proposed the following three hypotheses regarding the behavioral change and the brain plasticity from each training group. First, we hypothesized that AC training would show a superior beneficial effect on cognitive and auditory performances than would the other training groups because cognitive (tasks difficulty during training) and auditory (sound intensity level control) factors were changed based on participants' performance. For the brain plasticity, we also expected that AC training would alter regional gray matter volume (rGMV) and FC related to cognitive and auditory processes. For example, we expected brain plasticity in the bilateral temporal cortex (speech perception) (Peelle, 2019), the temporal pole (TP), and the precuneus, that are related to auditory processes (high listening effort) (Olson et al., 2007; Rosemann and Thiel, 2019). Moreover, we expected brain plasticity in the dorsal attention network (DAN) (Sanchez-Perez et al., 2019), prefrontal regions (Nissim et al., 2017), and medial temporal lobe (MTL), that are related to high cognitive processes (Tsukiura et al., 2002). Second, we assumed that the auditory training factor groups (ATFGs; the AC and A training groups) would show improvement in the auditory performance and the brain plasticity in the abovementioned auditory process-related brain regions. Third, we hypothesized that the cognitive training factor groups (CTFGs; the AC and C training groups) would show improvements in the cognitive performance and the brain plasticity in the abovementioned cognitive process-related brain regions because previous cognitive training studies have reported the beneficial effects of cognitive training on several cognitions in the healthy older adults (Nouchi et al., 2016b; Alnajjar et al., 2019).

EXPERIMENTAL METHODS

Ethics Statement

This study was registered in the UMIN Clinical Trial Registry (UMIN000042271). It was conducted between August 2019 and December 2019 in Sendai City, Miyagi Prefecture, Japan.

Participants were informed that the study was designed to investigate the effects of four training programs. The researchers who were not involved in generating the randomization sequence enrolled eligible participants and conducted pre-assessments. These participants were then randomly assigned to receive combination training (AC training group), single training (A training group or C training group), and no training (active control group). The researchers (who were not involved in generating the randomization sequence) enrolled and allocated participants to either the A (C training group), B (A training group), C (AC training group) or D (active control group) letters. The random allocation sequence was generated using an online computer program.[1] All participants engaged in their assigned training during in-person visits for 4 weeks. After training, the participants completed the post-training outcome assessments (**Figure 1**).

Participants

Fifty-six participants [13 men and 43 women; mean age = 68.07 years (standard deviation, *SD* = 4.14)] were recruited from the general population through advertisements in a local town paper and local newspapers (Kahoku Weekly). Interested participants were screened using a semi-structured telephone interview (10 questions) that approximately 10 min. The 10 questions pertaining to the inclusion and exclusion criteria were related to (1) age, (2) sex, (3) previous experience in intervention studies, (4) native language, (5) handedness, (6) subjective memory function, (7) history of medication use and disease (including hearing-related problems), (8) blood pressure, (9) history of diabetes, and (10) ability to complete training schedule.

[1]https://www.graphpad.com/quickcalcs/

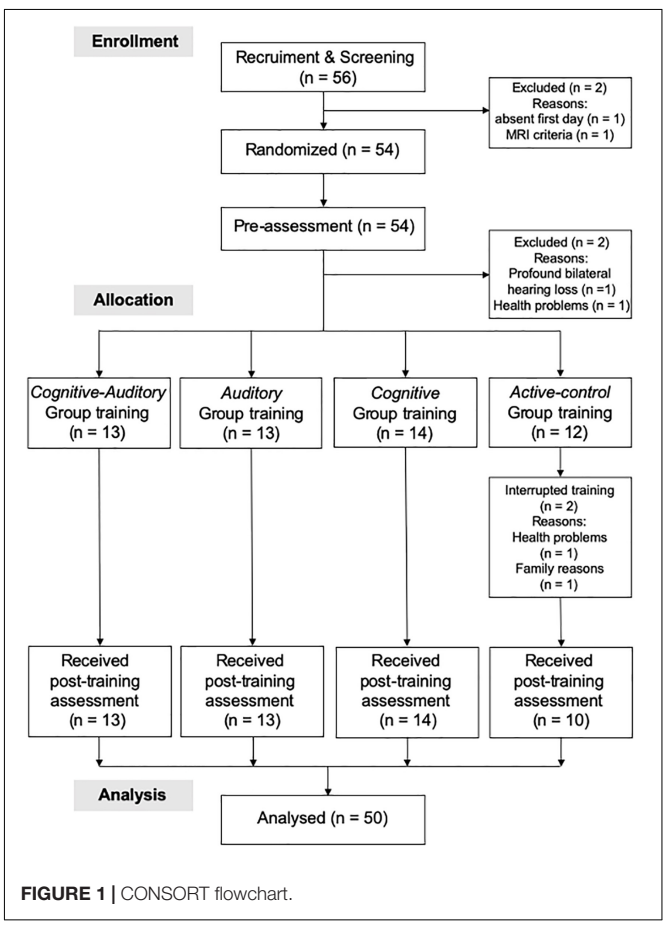

FIGURE 1 | CONSORT flowchart.

The participants were then invited to visit Tohoku University. We collected written informed consent from 55 participants (one participant did not visit the institution on the first day). Subsequently, all participants were subjected to a detailed auditory assessment [including assessment of PTA threshold and speech reception threshold (SRT)], cognitive function tests [such as the Mini-Mental State Examination (MMSE), LM, DS, and D-CAT], and MRI. None of the participants were excluded based on MMSE scores. However, two participants declined to participate before they were randomized into groups. One participant was excluded based on the auditory assessment (profound unilateral hearing loss), one participant was excluded because the MRI examination criteria were not met, and two participants declined to participate after initiating training (**Figure 1**).

Overview of Auditory Measures

To investigate the effect of auditory sensitivity after performed auditory training, we performed the PTA measurement, before and after the training. All participants underwent auditory assessment before starting the training schedule and after completing the eight training sessions at Tohoku University in a soundproof room. The PTA air conduction thresholds were measured using an audiometer (AA-76, RION, Tokyo, Japan) and standard headphones (AD-06B). The audiometer was calibrated in dB hearing level according to standards of the International Organization for Standardization (ISO/TC, 1996) and the American National Standard Institute (2019). Before PTA, all participants underwent an otoscopic examination to exclude occluded ear canals or other irregularities (i.e., no tympanic membrane abnormalities were observed). Each ear was assessed. Details of these measures are described in **Supplementary Material**.

Overview of Cognitive Function Measures

To measure the effects of cognitive training on each training group, participants performed the follow cognitive measures. Cognitive function was divided into four categories: general cognition, episodic memory, working memory, and attention. Global cognitive status was measured using the MMSE (Folstein et al., 1975). Episodic memory was measured using LM (Wechsler, 1987). Working memory was measured using DS (Wechsler, 1997). Attention was measured using D-CAT (Hatta et al., 2001). Details of these measures are described in **Supplementary Material**.

Magnetic Resonance Imaging Data Acquisition and Imaging Parameter

To acquire MRI data, we used a 3.0 Tesla Philips Achieva MRI scanner (Philips, Amsterdam, The Netherlands) with an eight-channel head coil at the Institute of Development, Aging and Cancer, Tohoku University. Fifty participants performed MRI before and after assessment. They were instructed to avoid moving their head. High-resolution T1-weighted structural images [240 × 240 matrix, time repetition (TR) = 6.6 ms, time echo (TE) = 3 ms, field of view (FOV) = 24 cm, slices = 162, and slice thickness = 1 mm] were collected using a magnetization-prepared rapid gradient-echo sequence. The quality of all imaging data was checked visually. The total scan time was 8 min. For the resting-state parameter, we used 34-transaxial gradient-echo images (64 × 64 matrix, TR = 2,000 ms, TE = 30 ms, flip angle = 70°, FOV = 24 cm, and slice thickness = 3.75 mm) covering the entire brain and acquired using an echo-planar sequence. For this scan, 160 functional volumes were obtained, while the participants were resting. The total scan time was 6 min. we utilized the same parameters as those used in a previous laboratory study (Takeuchi et al., 2012). During resting-state scanning, the participants were instructed to keep their eyes closed, stay as motionless as possible, not fall asleep, and avoid thinking about anything in particular.

Inclusion and Exclusion Criteria

Based on the previous intervention studies for older adults (Nouchi et al., 2019, 2021), the following participants were included: those who self-reported being right-handed, those who were native Japanese speakers; those who were unconcerned about their memory function; those who were not taking medications that interfered with cognitive function (such as benzodiazepines, antidepressants, and other central nervous system agents); those who did not have a history of diseases that affect the central nervous system, including thyroid disease, multiple sclerosis, Parkinson's disease, stroke, severe hypertension (systolic blood pressure > 180 mmHg and diastolic blood pressure > 110 mmHg), and diabetes; and those who were > 60 years old. Participants who had participated in other cognitive or auditory intervention studies were excluded. Participants with an MMSE score of < 26 (Folstein et al., 1975) or those with moderate-to-profound hearing loss were also excluded.

Training Materials

Four Training Groups

We set four training groups (AC training, A training, C training, and active control groups) (**Table 1**). All training groups performed three cognitive training tasks (short-term memory, working memory, and attention training tasks) with intensity level controlled audio stimuli (**Figure 2**). The short-term, working memory, and attention training tasks were developed based on our previous cognitive training studies (Nouchi et al., 2016a, 2019, 2020a, 2021, 2022; Takeuchi et al., 2020). Each cognitive training task had 4 task difficulty levels as a cognitive training factor [from level 1 (easy) to level 4 (difficult)]. Sound intensity level of auditory stimulus had 4 levels as an auditory training factor [from level 1 (easy) to level 4 (difficulty)].

The AC training group underwent a combination of cognitive and auditory training. In this group, the levels of the cognitive and auditory training factors were changed at the same time from level 1 to level 4 depending on the participants' performance.

In the A training group, the auditory training factor varied from level 1 to level 4 depending on the participants' performance. However, the cognitive training factor was not changed. The participants completed the three cognitive training tasks at level 1 difficulty of the cognitive training factor.

TABLE 1 | Based on the three cognitive task training (cognitive training factor) and audio stimuli intensity level control (auditory training factor), we set four training groups [auditory-cognitive training (AC), auditory training (A), cognitive training (C), active control groups].

Training group	Auditory training factor	Cognitive training factor
AC training	+	+
A training	+	−
C training	−	+
Active control group	−	−

The "+" symbol means that it contains variations in level difficulty. The "−" symbol means that it does not contain ant variation in the degree of level difficulty.

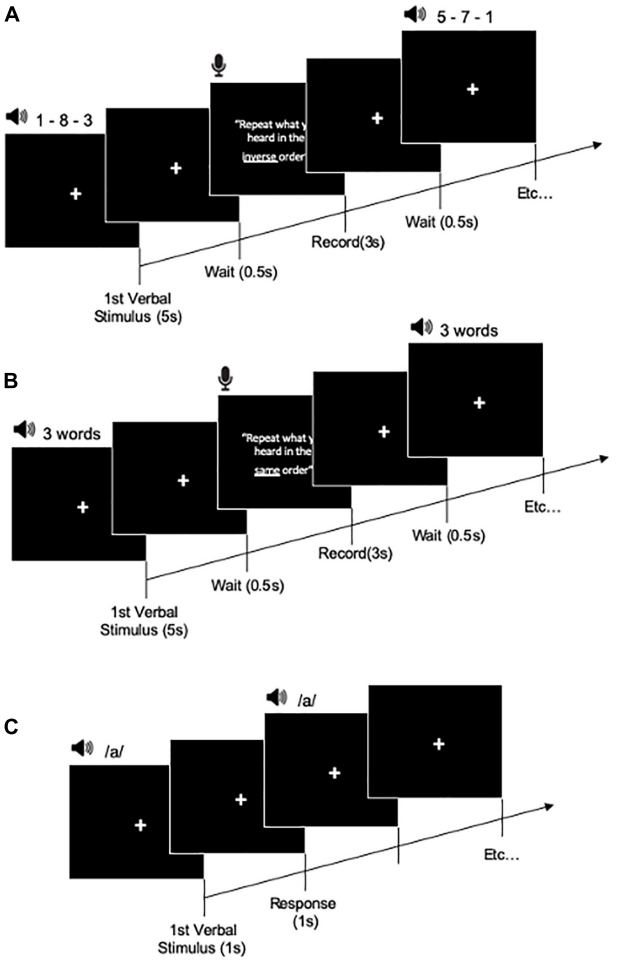

FIGURE 2 | Training task procedure for working memory training task **(A)**, short-term memory training task **(B)**, and attention training task **(C)**.

In the C training group, the cognitive training factor varied from level 1 to level 4 depending on the participants' performance. However, the auditory training factor did not change. The participants completed the three cognitive training tasks at level 1 of the auditory training factor.

In the active control group, there were no variations in the cognitive or auditory training factors. The participants completed the three cognitive training tasks at level 1 of cognitive and auditory training factors in all the training sessions.

Criteria of Level Change of Cognitive and Auditory Training Factors

We checked the participants' performance after each session. Levels of cognitive and auditory training factors were changed in every training session. The training level was increased when performance was $> 70\%$; it was maintained when the performance on the training tasks was 50–70% and was decreased by one level when the performance was $< 50\%$.

Manipulation of Sound Intensity Level of Auditory Stimulus

All three cognitive training tasks used auditory stimulus. Stimuli were presented in both ears. In the first session, all participants completed the three cognitive training tasks at level 1 of the auditory training factor. The level 1 of the auditory training factor differed among the participants because the level 1 of auditory factor was set based on the SRT at baseline.

For, the C training and active control groups the auditory training factor levels were not changed throughout the training sessions. They completed each cognitive training task at the level 1 of the auditory training factor. In the AC and A training groups, the sound intensity level of auditory stimuli for each cognitive training task was changed based on the cognitive training performance.

In this study, level 1 sound intensity level was set at SRT + 3 dB to SRT—3 dB. Level 2 sound intensity level was set at SRT + 0 dB to SRT—6 dB. Level 3 sound intensity level was set at SRT—3 dB to SRT—9 dB. Level 4 sound intensity level was set at SRT—6 dB to SRT—12 dB.

Details of Each Training Task

The subjects performed the tasks in the following order: short-term memory task, working memory task, and attention task. There were no criteria that decided the order. However, all subjects performed the same order. In addition, we selected the short-term/episodic memory training using words stimulus and working memory training using numbers stimulus based on previous cognitive training studies such as working memory training (Takeuchi et al., 2013) and short-term/episodic memory training (Ball et al., 2002). Also, to avoid a confusion of both training procedure, we used different types of stimuli between working memory training and short-term/episodic memory training. We expected that participants can easily understand the differences of training task procedure and perform trainings without confuse.

Short-Term and Episodic Memory Training Task

Short-term and episodic memory training task was performed using a word recall task. After listening to each list of words, the participants were asked to recall the words they could remember from the list in the same order. The recall of each trial was recorded. If all words were repeated in the correct order in a trial, then a score of 1 was given; if the response was incorrect in any way, then the trial was assigned a score of 0. In one

training session, the participants performed all the tasks three times for 5 min. Level 1 was composed of three words. Level 2 comprised four words. Level 3 included five words, and level 4 was composed of six words.

Working Memory Training Task

Working memory training task included the most commonly used listening span training. Participants listened (via headphones) to numbers and then recalled all numbers in reverse order. The recall was made orally and recorded. There was no time limit for responding. The subsequent trial started only when the participants pressed a button. If all digits in atrial were recalled in the correct order, then the trial was given a score of 1; if the response was incorrect in any way, then the trial was assigned a score of 0. In one training session, the participants performed all tasks three times for each task for 5 min. Level 1 of cognitive training was composed of three numbers. Level 2 was comprised four numbers. Level 3 was composed of five numbers, and level 4 six numbers.

Attention Training Task

In the attention training task (go/no-go attention task), the participants were presented one spoken vowel (i.e.,/a/) through headphones. The participants were instructed to press a "red button" key as quickly as possible each time a specific target vowel was presented. The response time (RT) and number of correct responses were recorded. In one training session, the participants performed the task three times for 5 min. Level 1 comprised one vowel and one target. Level 2 was composed of two vowels and one target. Level 3 involved three vowels and two targets. Level 4 was consisted of four vowels and two or three targets. The attention training task is similar task used in auditory attention training studies (Tallus et al., 2015).

Training Session Schedule

Each training session involved approximately 1 h of training per day was conducted 2 days per week for 4 weeks, resulting in a total of 8 session in predetermined order. The examiner and participants contacted each other by telephone in case of health problems (rescheduling the training date) and delays on the training session day. On the training day, it was possible to train two participants simultaneously for 1 h (two soundproof rooms were available).

Sample Size

No previous studies are using combined auditory and cognitive training on hearing ability, cognitive function, and brain plasticity in healthy older adults. Therefore, we did not conduct the sample size estimation for this study with accuracy. However, similar studies using cognitive training have been reported the improvements of cognitive functions after training. For example, the combined auditory and cognitive training with 16 participants led to the improvement in cognitive function (Yusof et al., 2019). Moreover, 4-week cognitive training study using 14 participants also reported cognitive improvements in processing speed and executive functions (Nouchi et al., 2012). For this reason, the present study was set from 14 to 16 participants in each group.

Analysis

Behavioral Data Analysis

Table 2 presents the baseline characteristics of the participants. We calculated the changes in scores (post-assessment score minus pre-assessment score) for all cognitive function tests and auditory assessments. Cognitive function measures and auditory measures were dependent variables. We used a two (the auditory training factor: with/without) by two (the cognitive training factor: with/without) factorial analysis covariance (ANCOVA) with permutation tests to investigate significant group differences in each cognitive function measure and auditory measure. All analyses were performed using the "aovp" function of the "lmPerm" package for changes in scores associated with each cognitive measure and auditory measure. We used the permutation ANCOVA test because it is suitable for small sample analysis and is freely distributed. Therefore, the permutation ANCOVA test is suitable and sufficiently powered for present study (Kulason et al., 2018; Nouchi et al., 2020b, 2022). The changes in scores in each group (AC training group, A training group, C training group, and active control group) were the dependent variables. All pre-assessment scores of the dependent variables, sex, age, and MMSE were used as covariates to adjust for background characteristics and exclude the possibility of any pre-existing difference in measures between the groups affecting the result. Fifty randomly allocated participants were included in the analyses. The level of significance was set at $p < 0.05$. The PTA threshold was the primary outcome. We applied the Bonferroni–Holm procedure (Holm, 1979) separately for cognitive measures (LM, D-CAT, and DS findings) and auditory measures (PTA threshold). All analyses are performed using the R software (RStudio Team, 2019) (R Core Development Team, Toulouse, France).

Additionally, participants in the active control group performed the baseline (level 1) in all sessions. In the behavioral analysis, we excluded the effect of active control on behavioral measures. Therefore, we excluded the possibility that the effect of active control had an impact on any outcome.

Image Preprocessing of Structural Brain Image

As a first step, we reviewed and converted all pre- and post-Digital Imaging and Communication in Medicine scans into the Neuroimaging Informatics Technology Initiative format using MRICRON software before running the analysis. All imaging data were analyzed using Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Cognitive Neurology; London, United Kingdom) implemented in MATLAB (MathWorks Inc., Natick, MA, United States). Briefly, SPM12 and Computational Anatomy Toolbox 12 (CAT12)[2] were used to create an asymmetric diffeomorphic anatomical registration through exponentiated Lie (DARTEL) algebra template from the original and flipped gray matter and white matter segments. T1-weighted structural images of each participant (pre- and post-imaging data) were segmented and normalized to the Montreal Neurological Institute (MNI) space using CAT12 to generate images with $1.5 \times 1.5 \times 1.5$ mm^3 voxel

[2]http://www.neuro.uni-jena.de/cat/

TABLE 2 | characteristics of participants in the AC training group, A training group, C training group, and active control group.

	AC-training group			A-training group			C-training group			Active control group			Max value
	Mean	***SD***	**95% CI**	**Mean**	***SD***	**95% CI**	**Mean**	***SD***	**95% CI**	**Mean**	**SD**	**95% CI**	
Global cognitive status													
MMSE (score)	28.77	1.05	[28.10, 29.42]	29.31	0.82	[28.79, 29.82]	29.36	0.81	[28.87, 29.84]	6.8	1.6	[26.59, 29.00]	30
Working memory													
DS (score)	7.07	2.26	[5.26, 8.30]	6.69	1.97	[5.44, 7.93]	6.78	2.54	[5.64, 8.50]	5.4	1.68	[4.12, 6.67]	16
Episodic memory													
LM (score)	10.46	3.02	[8.03, 13.11]	9.53	3.41	[7.39, 11.68]	10.57	4.36	[8.55, 12.36]	8.4	4.36	[5.10, 11.69]	25
Attention													
D-CAT (score)	172.9	21.44	[148.28, 190.64]	168.6	34.98	[146.60, 190.62]	174.8	44.22	[159.43, 186.41]	164.1	44.08	[130.85, 197.340]	200
Pure-tone audiometry													
PTA (dB)	16.44	7.58	[-2.80, 1.27]	16.54	6.28	[-2.08, 1.27]	21.43	10.71	[-2.41, 1.12]	23.88	7.86	[-2.46, 1.12]	90*

**Maximum output limits of the audiometer. AC, Auditory-cognitive training; A, auditory training; C, cognitive training; MMSE, Mini-Mental State Examination; DS, digit span; LM, logical memory; D-CAT, digit cancelation; PTA, pure-tone audiometry).*

size diffeomorphic anatomical registration through the DARTEL registration process. Moreover, we performed volume change correction (modulation). We used a SPM12 image calculator (ImCalc) to calculate the post-imaging value minus pre-imaging value for all participants. The required mask expression was (i2—i1).*(i2 > 0.1).*(i1 > 0.1). The mask expression was used to restrict the statistical analysis to regions of the brain expected to contain true signals. Subsequently, the generated rGMV image was smoothed using a Gaussian kernel of 8-mm full width at half maximum (FWHM).

Brain Structural Statistical Analysis

Full factorial model analysis was performed using SPM12 and CAT12. This approach was used to analyze the superior effects of AC training compared to other training groups, the effect of the auditory training factor (with/without), and the cognitive training factor (with/without). The main effects of both the factors and group comparisons were used as contrasts of interest (cognitive training factor main effect: AC + C > A + active control; auditory training factor main effect: AC + A > C + active control; the superior effects of AC training compared to other training groups: AC > A + C + active control). The model included two levels of each factor (cognitive and auditory training factors), age, sex, and total intracranial volume as covariates. Additionally, in the analysis of the superior effects of AC training compared to other training groups, we included the mask images (AC > C, AC > A, and AC > active control, a threshold of $p < 0.05$, uncorrected). Furthermore, we analyzed the relationship between behavioral changes scores (auditory and cognitive measures) and GMV. The covariates were mean centered, and we used threshold-free cluster enhancement (TFCE) with randomized (5.000 permutations) non-parametric testing using the TFCE toolbox.[3] We applied a cluster-level FWE-corrected at $p < 0.05$ (Takeuchi et al., 2012).

Preprocessing and Analysis of Resting-State Functional Connectivity

Resting-state FC preprocessing and analysis were performed using a standard pipeline in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012), implemented in MATLAB. Preprocessing included realignment, direct segmentation, normalization to the MNI space (2 mm^3), outlier detection (artifact detection tool based identification of outlier scans for scrubbing; motion correction = 0.9 mm; global-signal z-value threshold = 5),[4] and smoothing (FWHM = 8 mm). The realignment and scrubbing parameters and the BOLD signal from the WM and cerebrospinal fluid were regressed using a general linear model. Data were band-pass filtered at 0.008–0.09 Hz to reduce the effects of low-frequency drifts and high-frequency noise. First-level analyses included the calculation of individual whole-brain seed-to-voxel FC maps (Takeuchi et al., 2017).

Resting-State Functional Connectivity of Analysis

For second-level analysis, in the group-level comparisons, seed-based FC maps were used to analyze the superior effects of AC training compared to other training groups (AC > A + C + active control), main effect of the auditory training factor, and main effect of the cognitive training factor. We included the mask expression (AC > C, AC > A, and AC > active control, a threshold of $p < 0.05$, uncorrected). The brain seed regions were selected with reference to the results obtained in the brain structure analysis. Furthermore, we analyzed the relationship between behavioral changes scores (auditory and cognitive measures) and functional connectivity. We used TFCE with randomized (5.000 permutations) non-parametric testing using the TFCE toolbox (see text footnote 3). The clusters were threshold at an FWE corrected at $p < 0.05$ using a cluster-forming threshold of $p < 0.001$, which was uncorrected.

[3]http://dbm.neuro.uni-jena.de/tfce/

[4]https://www.nitrc.org/projects/artifact_detect

RESULTS

Behavioral Data

All participants had normal cognitive function, as indicated by MMSE scores [mean = 28.88, standard deviation (SD) = 1.22], and a normal to mild PTA threshold according to the Japan Audiological Society (mean = 19.23, *SD* = 2.95). Cognitive and auditory assessment scores before and after training in all groups are presented in **Figure 3**.

First, to investigate whether a group difference existed at the baseline (before training), we performed a two (the auditory training factor: with/without) by two (the cognitive training factor: with/without) ANCOVA with permutation tests for the baseline data. We did not find statistically significant interaction between the auditory and cognitive training factors {LM [$F_{(1,44)}$ = 0.49, p = 0.63, adjusted p = 0.85], D-CAT [$F_{(1,44)}$ = 0.17, p = 0.64, adjusted p = 0.85], DS [$F_{(1,44)}$ = 0.65, p = 0.51, adjusted p = 0.85], PTA [$F_{(1,44)}$ = 3.25, p = 0.08, adjusted p = 0.48]}. We did not find any significant effect of the auditory training factor {LM [$F_{(1,44)}$ = 0.02, p = 0.96, adjusted p = 0.96], D-CAT [$F_{(1,44)}$ = 0.04, p = 0.60, adjusted p = 0.48], DS [$F_{(1,44)}$ = 0.96, p = 0.23, adjusted p = 0.58], PTA [$F_{(1,44)}$ = 1.50, p = 0.17, adjusted p = 0.58]}, and the main effects of the cognitive training factor {LM [$F_{(1,44)}$ = 0.91, p = 0.26, adjusted p = 0.58], D-CAT [$F_{(1,44)}$ = 1.12, p = 0.9, adjusted p = 0.96], DS [$F_{(1,44)}$ = 1.37, p = 0.29, adjusted p = 0.58], PTA [$F_{(1,44)}$ = 0.021, p = 0.96, adjusted p = 0.96]}. The results indicated that the cognitive functions and auditory performance at baseline did not differ among the groups.

Second, we investigated effects of the interventions on cognitive function and auditory performance using the ANCOVA for changes in scores. We did not find statistically significant beneficial effects of AC training on PTA thresholds [$F_{(1,43)}$ = 0.72, p = 0.27, adjusted p = 0.40], LM [$F_{(1,42)}$ = 0.19, p = 0.38, adjusted p = 0.49], D-CAT scores [$F_{(1,42)}$ = 2.30, p = 0.06, adjusted p = 0.17], and DS [$F_{(1,42)}$ = 0.28, p = 0.92, adjusted p = 1.00] compared to other training groups. However, we found statistically significant main effects in the factor groups. In terms

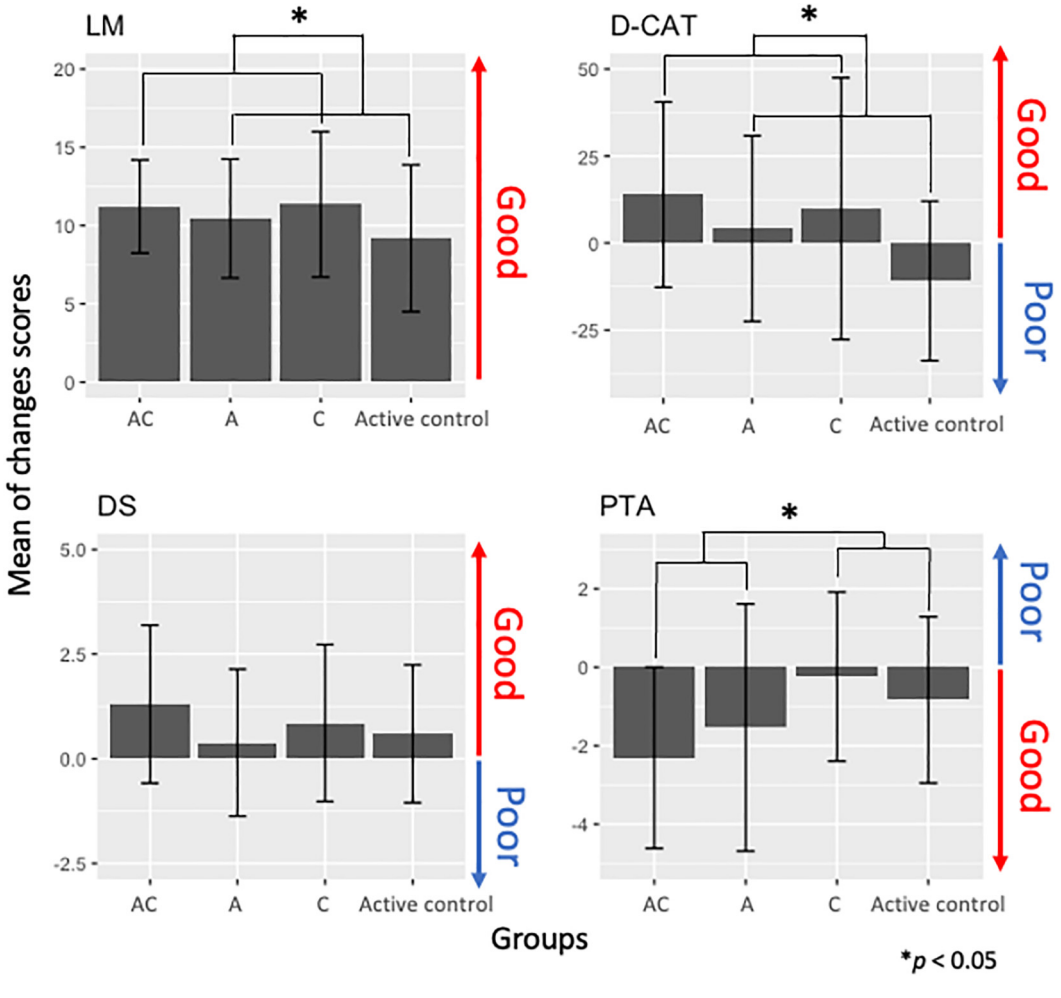

FIGURE 3 | Change scores in cognitive function measures [logical memory (LM), digit cancelation (D-CAT), digit span (DS)] and auditory [pure-tone auditory (PTA)] in each training group [auditory-cognitive training (AC), auditory training (A), cognitive training (C)].

of cognitive functions, the CTFGs (the AC and C training groups) had improvements in LM [$F_{(1,42)}$ = 5.15, p = 0.009, adjusted p = 0.04] and D-CAT scores [$F_{(1,42)}$ = 7.2, p = 0.006, adjusted p = 0.04] compared to the non-CTFGs (**Figure 3**). Moreover, the ATFGs (the AC and A training groups) had improved auditory performance [$F_{(1,42)}$ = 3.12, p = 0.02, adjusted p = 0.06] compared to the non-ATFGs (**Figure 3**).

Brain Structural Results

Only the AC training group showed changes between other training groups (A, C, and active control training groups) in rGMV in the right dorsolateral prefrontal cortex (R. DLPFC), the left inferior temporal gyrus (L. ITG), the left superior frontal gyrus (L. SFG), the left orbitofrontal cortex (L. OFC), and the right cerebellum (lobe 7 Crus 1) (FWE corrected at $p < 0.05$, **Figure 4** and **Table 3**). In addition, the ATFGs showed changes in the cluster located in the left temporal pole (L. TP) compared to the non-ATFGs (FWE corrected at $p < 0.05$, **Figure 4** and **Table 3**). Differences were observed in the clusters located in the right inferior occipital gyrus (R. IOG), right cerebellum (lobule 7 Crus 1) and R. ITG between the CTFGs and non-CTFGs (FWE corrected at $p < 0.05$, **Figure 4** and **Table 3**). In addition, we analyzed the relationships between behavior (cognitive and auditory) changes and brain structural changes. However, any changes of auditory and cognitive measures did not significantly correlate with brain structure changes.

Brain Functional Connectivity Results

The brain seed regions were selected based on the results obtained from the brain structure analysis. Thus, the AC training group showed no statistically significant changes compared to the other training groups. Compared to the non-ATFGs, the ATFGs had significantly increased FC between the TP and precuneus (**Figure 5** and **Table 4**). Compared to the non-CTFGs, the CTFGs showed no statistically significant changes compared with the other training groups. In addition, we analyzed the relationships between behavior changes and brain structural changes. However, any changes of auditory and cognitive measures did not significantly correlate with changes of brain functional connectivity changes.

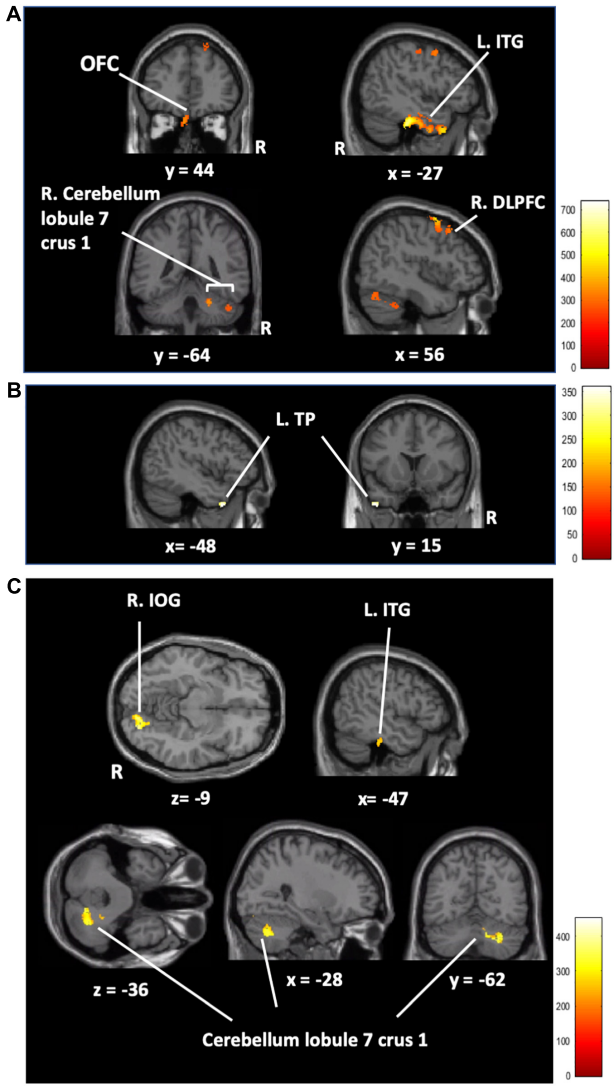

FIGURE 4 | (A) The regional gray matter volume results in the AC training group compared to that in the other training groups (AC > A + C + active control). The regional gray matter volume results of the auditory training factor main effect **(B)** and cognitive training factor main effect **(C)**. [Orbitofrontal cortex (OFC), left inferior temporal gyrus (L.ITG), right superior frontal gyrus (R.SFG), left temporal pole (L.TP), right inferior occipital gyrus (R.IOG), auditory-cognitive training (AC), auditory training (A), cognitive training (C)] FWE corrected at $p < 0.05$ based on 5,000 permutations. The color represents the strength of the TFCE values.

DISCUSSION

In this study, we investigated the beneficial effects of AC training on cognitive functions (via LM, D-CAT, and DS), auditory performance (via PTA), and MRI measures (brain structure and FC) in healthy older adults. We found three main results related to our hypotheses. First, AC training led to a change in rGMV in the frontal regions but did not improve cognitive and auditory performance compared to the other groups. Second, the ATFGs improved auditory performance (PTA threshold), changed the rGMV in the L. TP, and increased the FC between the L. TP and the precuneus compared to the non-ATFGs. Third, the CTFGs improved cognitive performance in terms of LM and D-CAT and changed the rGMV in the R. DLPFC, L. ITG, OFC, and right cerebellum (lobule 7 Crus 1) compared to the non-CTFGs. We have discussed these findings separately below.

In the first finding, AC training showed neural plastic changes in the rGMV, but did not improve any cognitive function or auditory performance compared to the other training groups. This finding partially supports our hypothesis. For neural plastic changes, we found that AC training increased the rGMV in the R. DLPFC, L. ITG, OFC, and right cerebellum (lobule 7 Crus 1). The DLPFC is suggested to be involved in central executive processes (Hertrich et al., 2021). Particularly relevant

TABLE 3 | Brain regional gray matter volume with a significant cluster in main effects analysis and group comparison analysis.

Anatomical location	Cluster size (mm^3)	Corrected *p*-value (FWE)	Peak MNI coordinates		
			x	y	z
AC > A + C + active control					
R. DLPFC	747	0.005	56	–5	51
L. ITG	2,554	0.001	–48	–27	–29
L. SFG	682	0.025	–48	6	53
L. OFC	184	0.017	–5	44	–32
R. Cerebellum Lobule 7 Crus 1	1,610	0.002	12	–87	–20
The main effect of the auditory factor					
L. TP	81	0.021	–48	15	–42
The main effect of the cognitive factor					
R. IOG	893	0.005	14	–81	–14
R. Cerebellum R. Lobule 7 Crus 1	35	0.036	38	–78	–23
ITG	71	0.032	–47	-29	–32

R. DLPFC, Right dorsolateral prefrontal cortex; L.ITG, left inferior temporal gyrus; L. SFG, left superior frontal gyrus; L. OFC, left orbitofrontal cortex; 7 crus1, cerebellum lobule; L. TP, left temporal pole; R. IOG, right inferior occipital gyrus; AC, auditory-cognitive training; A, auditory training; C, cognitive training) FWE corrected at p < 0.05.

to multiple tasks, the DLPFC is involved in scheduling processes in complex tasks (task management) (Smith and Jonides, 1999). Moreover, our results are consistent with previous findings in a multitasking cognitive training study (two or more cognitive activities at the same time); multitasking cognitive training using an auditory stimulus and a visual stimulus tasks increased the rGMV in the DLPFC in healthy young adults after a 4-week training period (Takeuchi et al., 2014). Additionally, previous neuroimaging studies have reported that the OFC, ITG, and cerebellum (lobule 7 Crus 1) are important for the integration of visual and auditory information (Wu et al., 2013; Nogueira et al., 2017; Lin et al., 2020). The OFC is thought to play an important role in adaptation to goal-directed behavior (Furuyashiki and Gallagher, 2007). During AC training, the participants had to integrate multisensory information during the combination of auditory and cognitive training factors. Therefore, the rGMV in the R. DLPFC, L. ITG, OFC, and right cerebellum (lobule 7 Crus 1) increased after 4 weeks of AC training. We did not find any significant beneficial effects of AC training on cognitive function and auditory performance compared to other training groups. This result is inconsistent with previous findings (Yusof et al., 2019). The training duration might be one of the reasons for this inconsistency, as the previous study had an 8-week intervention period, compared with the 4 weeks in the present study.

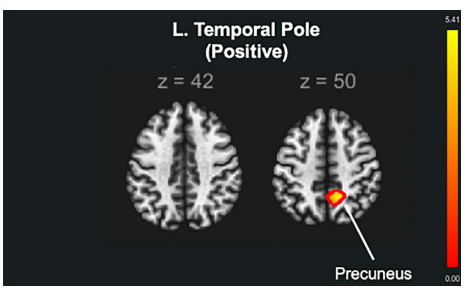

FIGURE 5 | The functional brain connectivity of the auditory training factor groups (ATFGs) compared to the non-ATFGs. The red color represents positive functional connectivity. FWE corrected at $p < 0.05$.

In the second finding, the ATFGs improved auditory performance (PTA threshold), changed rGMV-related speech perception, and increased brain connectivity in regions related to listening effort and language processing compared to the non-ATFGs. These findings support the second hypothesis of the present study. It was been previously reported that older adults could discriminate between words and sentences in high-noise situations after a 4-week training period (Karawani et al., 2016). However, the current study is the first to report that older adults can also listen to a sound with low intensity level, as shown with the PTA threshold.

The ATFG brain imaging results showed an increase in the rGMV in the left TP compared to that of the non-ATFGs. A previous fMRI study used sentence-listening tasks for normal hearing and listening difficulty (Stewart et al., 2020); it included three contrasts (phonology, intelligibility, and semantics). The phonology contrast showed bilateral activation in the middle and superior temporal gyrus, including the Heschl's gyrus and TP. Phonology is a system of processing the smallest units of speech sounds and their linguistic combinations. As per previous findings (Khalfa et al., 2001), the TP descending influence may improve the auditory afferent message by adapting the hearing function according to the cortical analysis of the ascending input. Previous studies, as well as the current study, have shown that listening to adverse conditions increases the activity of the anterior temporal cortex regions, specifically in the TP. In the present study, the participants in the ATFGs required auditory effort because the sound intensity level decreased during the

TABLE 4 | The peak MNI coordinates and intensity of brain clusters with significance in brain connectivity.

Network and seed region	Brain region	Cluster size (mm^3)	*p*-value FWE $p < 0.05$	Peak MNI coordinates(X, Y, Z)			Direction of correlation
The main effect of the auditory factor							
L. TP	Precuneus	184	0.019892	+ 12	–52	+ 50	Positive

L. TP, Left temporal pole; AC, auditory-cognitive training; A, auditory training; C, cognitive training. FWE corrected at $p < 0.05$.

auditory training task. In terms of FC, the ATFGs showed a significant increase in FC between the L. TP and precuneus compared to the non-ATFGs. The FC between the TP and precuneus is reportedly important in hearing sounds in situations requiring high auditory effort (Rosemann and Thiel, 2019). A study has suggested that the FC between the TP and precuneus is associated with auditory effort (Rosemann and Thiel, 2019). In the ATFGs, the participants focused on low sound intensity level during the auditory training tasks. Therefore, FC between the TP and precuneus was comparable between the ATFGs and non-ATFGs.

In the third finding, the CTFGs improved cognitive performance and increased the rGMV in the R. ITG, R. IOG, and right cerebellum (lobule 7 Crus 1) compared to the non-CTFGs. These results support the third hypothesis in present study. For cognitive improvements, the CTFGs showed significant improvements in the LM and D-CAT. Multiple cognitive training usually presents better results than single cognitive training (Auffray and Juhel, 2001). In addition, previous studies that used cognitive training reported near transfers in cognitive function (Golino et al., 2017). In this study, our cognitive training included several cognitive components, such as attention, episodic memory, and working memory. Therefore, we found significant improvements in episodic memory and attention performance.

The CTFGs showed a significant increase in the rGMV in the R. ITG, R. IOG, and right cerebellum (lobule 7 Crus 1) compared to the non-CTFGs. Previous functional neuroimaging studies have shown that the L. ITG should be recruited more for the maintenance of words than pseudowords (Fiebach et al., 2006). In studies of language processing, the ITG has also been associated with prelexical processing of abstract word form (Cohen et al., 2000) and conceptual semantic processing (Herbster et al., 1997), independent of presentation modality (Cohen et al., 2004). The previous training study supports the suggestion that the cerebellum may be important for shifting performance from the attentionally demanding stage to a more automatic state (Holtzer et al., 2017). Previous neuroimaging studies have reported that the ITG and cerebellum (lobule 7 Crus 1) are associated with information integration (Wu et al., 2013; Nogueira et al., 2017; Lin et al., 2020). Additionally, a previous study reported that activity occurs in the IOG during tasks that require episodic memory usage (Matthaus et al., 2012). The participants in the CTFGs were required to exert more cognitive effort as the cognitive training tasks increased in difficulty. Therefore, brain imaging results showed an increase in the rGMV in the R. ITG, R. IOG, and right cerebellum (lobule 7 Crus 1).

The present study had some limitations. First, AC training had fewer beneficial effects on behavioral performance compared to other training modalities. However, we found positive effects on the brain structure and FC. A possible explanation for this could be the different measurement indices used (cognitive, auditory, and brain) had an effect. Second, we did not consider the effects that could occur over time after training. Third, the present study did not evaluate the beneficial effects of training on quality of life. As mentioned previously, ARHL causes a cascade of deficits that can lead to dementia. Thus, after the present training, the participants may have affected communicating in quality of life and change in social isolation. It would be beneficial is a future study would consider the quality of life effects of AC training. Fourth, the PTA was used to assess auditory sensitivity, but the cognitive potential noted cannot be excluded. Fifth, the auditory and cognitive training factors increased the level of difficulty in the training groups relative to the subject's performance. However, the auditory training factor may partially lead to a change in the difficulty of the cognitive task, especially considering that the study group consisted of older adults. Sixth, for the working memory and short-term/episodic memory tasks, it is also necessary to check whether the same effect can be achieved by changing the stimulus of the training task. Final limitation is the small number of participants. Due to the small sample number of samples, it is hard to generalize the current results into general a population. This is a first step in the overall research on AC training using low sound intensity level as auditory training task. In the future study it is important to conduct a large sample RCT to investigate beneficial effects of AC training on auditory and cognitive performance as well as neural plasticity.

Hearing aids are the first choice for people with hearing loss and have made significant technological advances over the last two decades. Although satisfaction with hearing aids has improved, hearing aid users often encounter difficulties in challenging listening conditions (Ohlenforst et al., 2017). The disadvantages of hearing aids include the following: (1) they do not block background noise, (2) separate speech from sounds in noisy environments, and (3) they allow users to hear sounds at a distance (Ohlenforst et al., 2017). Thus, the current auditory training method have important implications for the clinical management of people with deterioration in auditory processing. The present study showed that the auditory training to increase auditory performance. Especially, AC training changed the brain structure in the DLPFC and ITG, which are associated with working memory and auditory processing. We believe that this study has implications for improving auditory performance in older adults. In addition, the present training methods may improve auditory sensitivity and alter brain structure and functional connectivity.

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 human participants were reviewed and approved by the Institutional Review Board at the Tohoku University of Sendai, Japan. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NYSK: conceptualization, data curation, formal analysis, investigation, visualization, writing—original draft, and writing—review and editing. RN: conceptualization, investigation, methodology, validation, visualization, writing—original draft, and writing—review and editing. KO and YM: investigation, writing—review and editing. RK: supervision and writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Relationships Among Temporal Fine Structure Sensitivity, Transient Storage Capacity, and Ultra-High Frequency Hearing Thresholds in Tinnitus Patients and Normal Adults of Different Ages

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Background: Elderlies and tinnitus patients often find it challenging to process acoustic signals in noisy environments. The sensitivity to temporal fine structure (TFS), the transient storage capacity for TFS, and the ultra-high frequency (UHF) thresholds are all associated with aging-related damage, evidenced by speech-in-noise perception deficits. In the present study, we aimed to investigate the relationships among TFS sensitivity, transient storage capacity, and UHF thresholds in tinnitus patients and normal adults of different ages.

Methods: In the present study, 38 tinnitus patients (age ranging from 21 to 65) and 23 non-tinnitus adults (age ranging from 22 to 56) were enrolled, and some of their auditory indicators were examined, including the TFS-adaptive frequency (TFS-AF), break in interaural correlation (BIAC) delay threshold, and UHF thresholds.

Results: We found no significant difference in TFS-AF thresholds and BIAC delay thresholds between the tinnitus group and normal group, while their relationships with age were more evident in the tinnitus group. Moreover, these two tests were only significantly correlated in the tinnitus group. UHF thresholds were significantly correlated with TFS-AF thresholds only in the tinnitus group, suggesting that the UHF hearing was positively associated with the TFS sensitivity.

Conclusion: These findings indicated that the influencing factors, such as tinnitus and UHF thresholds, should be fully considered when examining age-related hearing decline, because the combination of tinnitus and poor UHF hearing might play a role in affecting hearing ability, such as TFS sensitivity.

Keywords: tinnitus, temporal fine structure, break in interaural correlation, ultra-high frequency, aging

INTRODUCTION

Tinnitus refers to the feeling of conscious ringing in the ear without a corresponding external sound source or electrical stimulation. It is a common clinical symptom with increasing prevalence. A meta-analysis shows that the prevalence of tinnitus ranges from 11.9 to 30.3% using the same definition of tinnitus (McCormack et al., 2016). In this meta-analysis, 26 studies report the prevalence of tinnitus by different age groups and generally show an increasing prevalence with age. Therefore, tinnitus remains an essential underlying factor in determining the effect of aging on hearing ability.

Many people with normal audiograms have hearing problems, and tinnitus patients show impaired speech-in-noise (SiN) perception (Gilles et al., 2016). Deficits in speech perception for tinnitus patients and/or older people with normal audiograms probably reflect that age and tinnitus are independent factors associated with poorer speech perception. Animal studies indicate that the "hidden hearing loss" phenomenon may be related to the massive loss of inner hair cell synapses caused by acoustic overexposures (Liberman and Liberman, 2015). Additionally, hearing loss can occur in higher frequency ranges, and studies have found that a majority of tinnitus patients with normal hearing thresholds up to 8 kHz have hearing impairment above 8 kHz (Vielsmeier et al., 2015), which is also common in the non-tinnitus population (Waechter et al., 2021). The ability to process temporal fine structure (TFS) information, including the sensitivity (Moore and Sek, 2009; Moore et al., 2012; Perez Vallejos et al., 2014; Füllgrabe and Moore, 2018) and storage capacity (Huang et al., 2009; Li et al., 2013; Liu et al., 2016) of TFS, is another aspect of suprathreshold processing that has received considerable attention in recent years.

In the cochlea, broadband sound, such as speech, is decomposed into several narrowband signals, and these signals can be considered as the relatively slow variation in amplitude over time (envelope, ENV) and the rapid oscillations with a rate close to the center frequency of the band (TFS) (Moore and Sek, 2009). The processing ability of TFS is essential for basic auditory functions, such as unmasking and localization of sound source. ENV is most important for speech perception, and TFS is most important for sound localization and pitch perception, revealing the acoustic basis for the "what" and "where" pathways in the auditory cortex (Smith et al., 2002).

Among the many auditory-related indicators, the ability related to TFS declines quickly with age. By using the TFS1 test (Moore et al., 2012), TFS2 test (a modified version of the TFS1 test by using a narrower passband) (Hopkins and Moore, 2011), TFS-LF (low-frequency) test (Füllgrabe and Moore, 2018), and TFS-AF (TFS-adaptive frequency) test (Füllgrabe et al., 2018), studies have shown that TFS sensitivity declines with age in the absence of elevated audiometric thresholds or broadened auditory filters. Among these methods, the TFS-AF test has many advantages and is the most recommended measurement of fine structure sensitivity (Füllgrabe et al., 2018). Multiple factors can predict TFS sensitivity. A meta-analysis shows that audiometric threshold and age only account for up to 42% of the variance in binaural TFS sensitivity, leaving a substantial variance to be explained by other factors, such as cognitive abilities (Füllgrabe and Moore, 2018). Among various cognitive abilities, working memory capacity is involved in temporal auditory processing (Troche and Rammsayer, 2009; Broadway and Engle, 2011). Studies have found that working memory is related to the high-frequency hearing threshold (10–16 kHz), while the presence of tinnitus may not impair the working memory test (Waechter et al., 2019, 2021).

Similarly, the storage capacity for TFS (as primitive auditory memory in many studies, PAM) also declines with age (Li et al., 2009). In a noisy and reverberant environment, people can still recognize and understand the voice of the target speaker. This common phenomenon reflects the remarkable ability of the brain to use various spatial (and/or non-spatial) cues to facilitate selective attention to target speech and follow the target stream against irrelevant influences (Cherry and Colin, 1954). To perceptually separate the target signal from other disruptive sound signals, the auditory system needs to separate the sound of the target and interfering sources and integrate the target sound wave that directly comes from the target source with its reflections, depending on the similarity between the leading direct and the lagging reflections (Li et al., 2005; Huang et al., 2008). However, due to the direct-reflection delay, faithful storage of TFS signals of the leading sound waves in the central auditory system is required for the computation of the similarity (Huang et al., 2009). Theoretically, faithful storage of TFS signals of the leading wave is necessary for both the central computation of the similarity and the perceptual integration between the leading and lagging waves. This faithful auditory storage of TFS has been recognized as the early point in the chain of the transient auditory memory system and termed as PAM (Li et al., 2013).

Primitive auditory memory can be measured using behavioral methods. Humans are extremely sensitive to the dynamic changes in interaural correlation, such as detecting a dynamic break in interaural correlation (BIAC, a brief drop of interaural correlation from 1 to 0 and then return to 1) in a steady-state noise (Akeroyd and Summerfield, 1999; Boehnke et al., 2002). Introducing a change in interaural correlation does not alter the monaural energy spectrum of the sound signals but changes dichotic repetition pitch (Bilsen and Goldstein, 1974) and the loudness (Moore, 2003) of the noise. Furthermore, even if a binaural time interval is introduced, humans can still detect the presence of BIAC (Li et al., 2013). By increasing the time interval, a threshold can be found, and participants cannot detect BIAC beyond this threshold. This measured binaural delay threshold represents the ability of PAM, which is the maximum retention time of TFS (Kong et al., 2012, 2015).

Taken together, in the normal population, both sensitivity and storage capacity for TFS decline with age, and these studies generally do not consider the effects of tinnitus or ultra-high frequency (UHF) threshold. In the present study, we

examined the relationships among age, the sensitivity and storage capacity of TFS, and the UHF threshold in the tinnitus group and normal group.

MATERIALS AND METHODS

Participants

A total of 61 adults participated in this study, including 38 patients with chronic subjective tinnitus (19 males and 19 females, age ranging from 21 to 65, with a mean of 45.08 years and a standard deviation of 11.04) examined in Tianjin First Central Hospital (Tianjin, China), and 23 non-tinnitus people (11 males and 12 females, age ranging from 22 to 56, with a mean of 35.26 years and a standard deviation of 11.26) from nearby communities. Kolmogorov-Smirnov tests showed that age obeyed a normal distribution in both tinnitus group and normal group (for tinnitus group: K-S Z scene = 0.771, p = 0.591; for normal group: K-S Z score = 0.766, p = 0.600).

Each participant underwent otoscopy and immittance measures by a certified audiologist in otoscopy and tympanometry. Otoscopic examinations had to reveal clear ear canals for all participants. Tympanograms were carried out using a 0.226-kHz probe tone and a pressure change in the ear canal equal to 200 daPa/sec. Resultant peak admittance, peak pressure, tympanometric width, and ear canal volumes had to be within normal ranges. Participants had to have a detectable acoustic reflex ($>$0.02 mmho) at 1 kHz evoked by contralateral stimulation. Pure-tone thresholds were collected by certified audiologists using pulsed tones at 125 Hz, 250 Hz, 500 Hz, 1, 2, 4, and 8 kHz. UHF behavioral thresholds were obtained at 10, 12.5, 16, and 20 kHz.

Written informed consent was obtained from all participants, and a modest stipend was given for their participation. The study was approved by the Tsinghua University Ethics Committee.

Apparatus and Stimuli

Each participant sat comfortably in a chair in a sound-attenuated room, and the test environment was in compliance with the requirements of ISO 8253-1:2010. All the acoustic signals, calibrated by a sound-level meter (AUDit and System 824, Larson, Davis, CA, United States), were delivered using the Creative Sound Blaster (Sound Blaster X-Fi Surround 5.1 Pro, Creative Technology Ltd., Singapore) and presented to participants over the two earpieces of Sennheiser HD650 headphones.

Daily calibration was completed for each pair of earphones (conventional and UHF transducers) using electro-acoustic ear simulators. A complete acoustic calibration (industry standard) of all equipment was performed prior to, twice during, and after data collection. Tympanometry was completed using GSI TympStar Pro. Conventional behavioral thresholds and high-frequency behavioral thresholds were obtained with GSI AudioStar Pro audiometers.

All participants were subjected to test for pure-tone hearing threshold first. The order of the BIAC delay threshold and TFS-AF tests was randomized between participants. Before each test, there would be a practice phase to ensure that participants understood the experimental task (details of the practice phase are described below).

Test for Break in Interaural Correlation Delay Threshold

The storage capacity of TFS was determined by the BIAC delay threshold test. The parameters and procedures of the BIAC delay threshold test have been described in detail in previous studies (Li et al., 2013; Lei and Ding, 2021). In the testing stage of the BIAC delay threshold, Gaussian wideband noises (2,000 ms in duration, including 30-ms rise-fall time) were synthesized using the "randn()" function in the MATLAB function library (the Math Works Inc., Natick, MA, United States) at the sampling rate of 48 kHz with a 16-bit resolution. The intensity of the noise stimulus was set at 60 dB sound pressure level (SPL). In one presentation, the left-headphone noise was an exact copy of the right-headphone noise. In the other presentation, the left-headphone noise was also identical to the right-headphone noise except that its temporal middle was substituted with a randomly selected independent noise fragment (e.g., the BIAC) with a fixed duration of 200 ms before filtering. Therefore, a brief break of interaural correlation, from 1 to 0 and then return to 1, was introduced. The offset-to-onset interval between the two presentations was 500 ms. In each presentation, the noise presented through the right headphone always started simultaneously with or led that presented through the left headphone.

Before the BIAC test, all the participants became familiarized with binaurally presented noise either with or without the BIAC. Subsequently, the participant initiated a trial by pressing the computer mouse, and the task was to identify which of the two presentations contained the BIAC. The longest interaural interval (IAI) for BIAC detection was measured using a three-up-one-down paradigm (Levitt, 1971). The IAI started from 0 ms, and then it was increased following three consecutive correct identifications of the presentation containing the BIAC and decreased following one incorrect identification. The initial step size of changing the IAI was 16 ms, which was altered by a factor of 0.5 with each reversal of direction until the minimum size of 1 ms was reached. Visual feedback was given after each trial to indicate whether the identification was correct or not. The test session was terminated following 10 reversals in direction, and the longest IAI was defined as the mean IAI for the last six reversals.

Test for the Sensitivity of Temporal Fine Structure

In the testing stages of TFS-AF, this study used a special software package published by Moore on the Internet[1] (Sęk and Moore, 2020) with most parameters at the default settings (Sęk and Moore, 2012).

Temporal fine structure-adaptive frequency test is a new method to determine the binaural sensitivity to TFS

[1]https://www.psychol.cam.ac.uk/hearing

(Füllgrabe et al., 2017). Two consecutive intervals were presented on each trial, separated by 500 ms. Each interval contained four consecutive 400-ms tones, separated by 100 ms. In one interval, the first and third tones were the same, while the second and fourth tones differed in their interaural phase difference (IPD) by φ (the target). Participants sensitive to binaural TFS perceive pure tones with a sufficiently large IPD lateralized toward one ear. In the other interval, the IPD of all tones was always 0° (the standard), while tones with IPD = 0° were perceived as emanating from close to the center of the head. Participants were asked to indicate which of the two intervals contained a sequence of tones that appeared to move within the head. The frequency was adaptively adjusted. The TFS-AF test used a two-up-one-down to estimate the 71% correct point on the psychometric function. If the participants chose twice in the right choices, the frequency would increase, and otherwise, it would decrease. The initial magnification was changed by 1.4 times, the first reversal was 1.2 times, and the third and subsequent times were 1.1 times. The test was terminated after eight reversals, and the geometric average of the last six inflection points was used as the threshold estimate. For the TFS-AF test in this study, the initial frequency was 200 Hz, the sound intensity of the left and right ears was 30 dB SPL, and the phase difference (φ) was set to 180°.

In the practice run of the TFS-AF test, the participants could choose to listen to four tone bursts (200 Hz) all with an IPD of 0° ("Not Moving") or to four bursts that alternated between an IPD of 0° and an IPD of 180° ("Moving"). When the participant was satisfied that they could hear the difference between "Not Moving" and "Moving," they could finish the practice run. All the results were automatically output by the software after the test.

It should be noted that the BIAC delay threshold test used the three-up-one-down procedure. In contrast, the TFS-AF test used the two-up-one-down procedure, which was consistent with past studies and could facilitate horizontal comparison with the results of past studies.

RESULTS

Ultra-High Frequency Hearing Thresholds in Healthy Controls and Tinnitus Patients

Air-conduction pure-tone audiometric thresholds were assessed following the procedure recommended by the British Society of Audiology (2004) and using standard calibrated audiometric equipment. **Figure 1** presents the results of pure-tone hearing thresholds for each participant. We included the UHF range in the measurement of pure-tone hearing. Several participants with poor pure-tone hearing were not excluded, in order to present the data as completely as possible. After excluding four participants whose pure-tone hearing threshold below 4 kHz was higher than 35 dB, the experimental results of this study remained unchanged.

Spearman correlation analyses showed that the pure-tone averages (PTA) were significantly decreased with age in both the normal group (for $PTA_{0{\cdot}125-1\ kHz}$: $r = 0.597$, $p = 0.003$; for $PTA_{2-8\ kHz}$: $r = 0.596$, $p = 0.003$; for $PTA_{10-20\ kHz}$: $r = 0.706$, $p < 0.001$) and tinnitus group (for $PTA_{0{\cdot}125-1\ kHz}$: $r = 0.362$, $p = 0.025$; for $PTA_{2-8\ kHz}$: $r = 0.384$, $p = 0.017$; for $PTA_{10-20\ kHz}$: $r = 0.675$, $p < 0.001$). **Figure 2** shows the age-related changes in $PTA_{10-20\ kHz}$ in the normal group and tinnitus group. Overall, the correlations between age and pure-tone averages were systematically lower in the tinnitus group than in the normal group.

Distribution of Temporal Fine Structure-Adaptive Frequency and Break in Interaural Correlation Delay Thresholds With Age

One participant in the normal group failed to complete the BIAC delay threshold test, and one participant in the tinnitus group failed to complete the TFS-AF test. These two participants were excluded from subsequent analyses involving correlation. Kolmogorov-Smirnov tests showed that both the BIAC delay threshold and TFS-AF threshold followed a normal distribution (for BIAC: K-S Z scene = 0.713, $p = 0.690$; for TFS-AF: K-S Z score = 0.881, $p = 0.419$). Two independent sample t-tests did not find any significant difference in both the BIAC delay thresholds and TFS-AF thresholds between the tinnitus group and normal group (for BIAC: $t(58) = 1.026$, $p = 0.309$; for TFS-AF: $t(58) = 0.062$, $p = 0.950$). For the normal group, the mean BIAC delay threshold was 7.64 ms (SD = 4.50 ms), and the mean TFS-AF threshold was 914.83 Hz (SD = 393.77 Hz). For the tinnitus group, the mean BIAC delay threshold was 6.67 ms (SD = 2.81 ms), and the mean TFS-AF threshold was 907.28 Hz (SD = 488.66 Hz). **Figure 3** shows the distribution of the BIAC delay threshold and TFS-AF threshold at different ages. Four independent Spearman correlation analyses were used. After Bonferroni's correction, the BIAC delay threshold was significantly decreased with age in the normal group. Both the BIAC delay threshold and TFS-AF threshold were significantly decreased with age in the tinnitus group.

The Relationship Between Temporal Fine Structure-Adaptive Frequency and Break in Interaural Correlation Delay Thresholds

Temporal fine structure-adaptive frequency measures the sensitivity of TFS, while the BIAC delay threshold test mainly determines the preservation capacity of TFS. Therefore, measured scores of BIAC delay thresholds may be related to TFS sensitivity. To explore such a possibility, we analyzed the relationship between the BIAC delay threshold and TFS-AF threshold using Spearman correlations. **Figure 4** shows that the TFS-AF threshold was significantly correlated with the BIAC delay threshold in the tinnitus group but not the normal group. This finding might be attributed to the fact that some patients in the tinnitus group had a significant decrease in TFS sensitivity

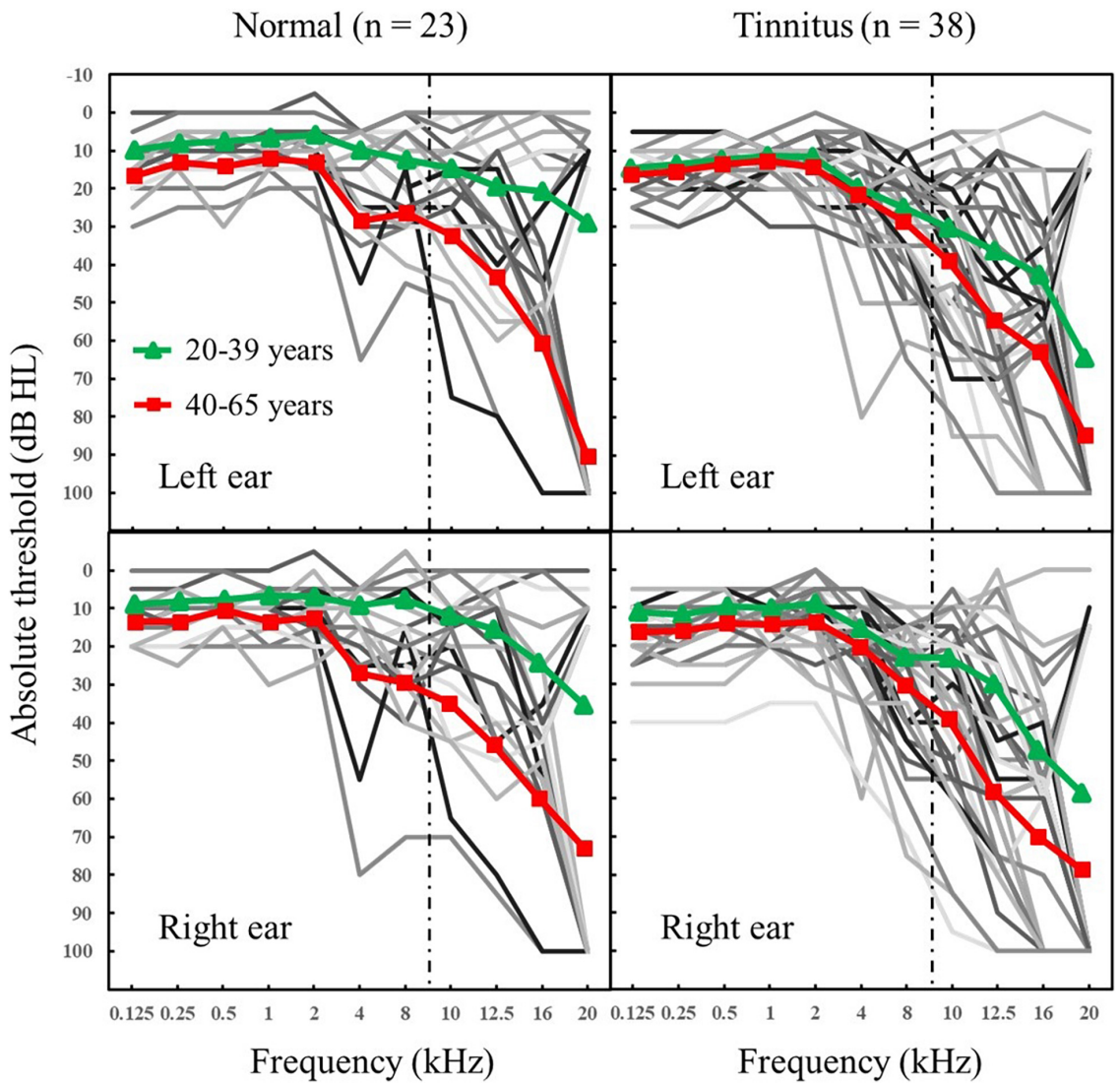

FIGURE 1 | Individual (thin lines) and mean (filled symbols and thick lines) audiometric thresholds (in dB hearing level [HL]) for frequencies between 0.125 and 20 kHz for each ear and two groups: normal group without any tinnitus; tinnitus group. To the right of the dashed line is the UHF range. Triangle symbol: 20–39 years; Square symbol: 40–65 years.

and storage capacity, leading to a higher correlation between the BIAC delay thresholds and TFS-AF thresholds.

The Relationship Between Ultra-High Frequency Hearing Thresholds and Temporal Fine Structure-Adaptive Frequency and Break in Interaural Correlation Delay Threshold

Studies have explored the relationship between TFS-AF and pure-tone hearing below 8 kHz (Füllgrabe et al., 2018). However, pure-tone hearing above 8 kHz may also affect the processing of TFS. Correlations were calculated between BIAC delay thresholds, TFS-AF thresholds, and UHF hearing thresholds for the normal group and tinnitus group to explore other potential contributors to the individual variability in BIAC delay thresholds and TFS-AF thresholds. Spearman correlations were used to avoid non-normal distribution. **Table 1** shows the results and associated significance levels. Spearman correlation analysis showed that the TFS-AF threshold was significantly correlated with the PTA of UHF threshold in the tinnitus group, suggesting that UHF hearing was positively associated with TFS sensitivity.

DISCUSSION

In noisy, reverberant environments, the elderlies often find it challenging to process acoustic signals, even though they can function well in quiet environment (Stuart and Phillips, 1996). Many studies have analyzed possible causes and influencing

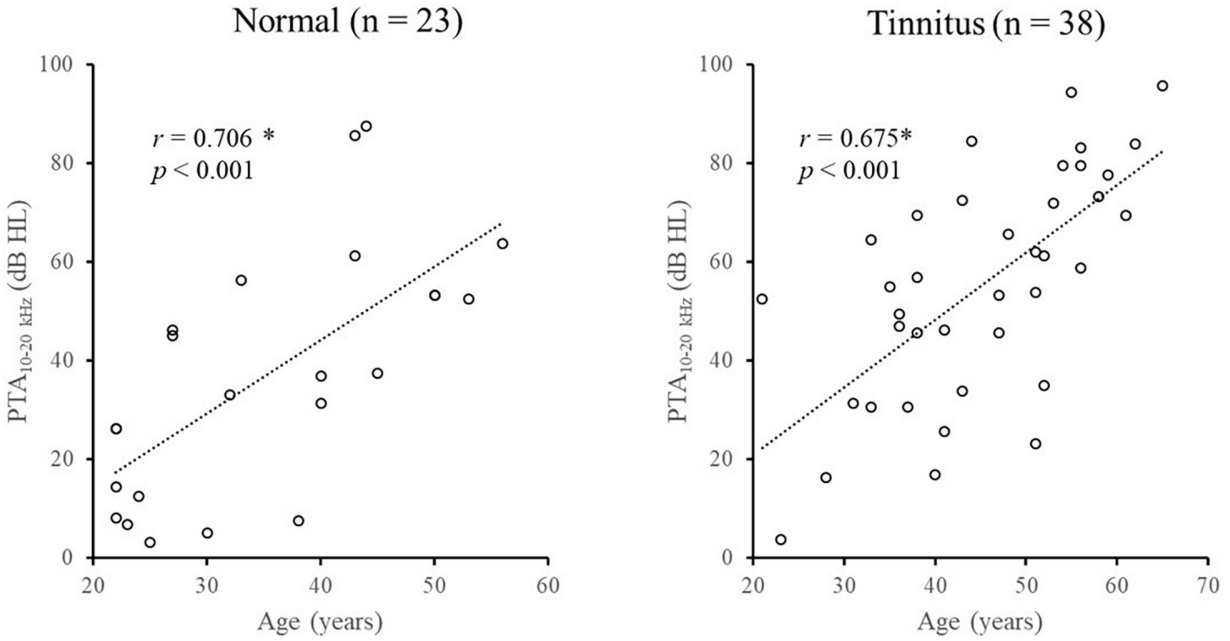

FIGURE 2 | Illustration of the age-related changes in $PTA_{10-20\ kHz}$ in the normal group and tinnitus group. *Significant effect after Bonferroni's correction, $p < 0.008$.

factors from different perspectives. First, the sensitivity to monaural/binaural TFS is poorer for elderlies compared with younger adults, and this may contribute to age-related declines in the ability to understand speech in noisy situations (Hopkins and Moore, 2011; Moore et al., 2012; Füllgrabe et al., 2015; Füllgrabe and Moore, 2018). Second, detecting a change in correlation is an essential component of scene parsing. For correlation comparison, temporary storage of sound's waveform (mainly TFS) is necessary (Li et al., 2013). Third, the representation of aspects of the TFS decays more rapidly in elderlies compared with younger adults (Li et al., 2009), suggesting that elderlies can not be as capable as younger adults in parsing auditory scenes. Finally, tinnitus patients show decreased SiN reception (Gilles et al., 2016), and high-frequency audiometry (>8 kHz) provides relevant additional information in tinnitus patients using conventional audiometry (Vielsmeier et al., 2015). Exploring the relationship between these factors can help understand age-related auditory perception changes in noisy situations.

Recently, more attention has been paid to the symptoms of tinnitus due to the increasing number of tinnitus patients (Dawes et al., 2014). Auditory acuity above 8 kHz is significantly associated with speech intelligibility in noise (Yeend et al., 2017; Zadeh et al., 2019; Trine and Monson, 2020), and UHF impairment may be associated with tinnitus (Vielsmeier et al., 2015). In addition, many hearing-related studies indicate that the participants have normal pure-tone hearing thresholds. Some of these participants may have hearing loss in the UHF range, affecting the measurement of some hearing indicators.

Several recent studies have reported that tinnitus patients and normal controls perform comparably well in cognitive tests when the hearing status is controlled (Waechter and Brännström, 2015; Waechter et al., 2019, 2021; Glick and Sharma, 2020; Hamza and Zeng, 2021; Jensen et al., 2021). In addition, part of the variance in TFS sensitivity is associated with factors such as cognitive abilities (Füllgrabe and Moore, 2018), suggesting that the tinnitus group and normal group do not differ significantly in terms of TFS sensitivity.

In the present study, the BIAC delay threshold was correlated with age in both the normal group and tinnitus group, which was consistent with previous studies (Li et al., 2009). Studies have found that younger listeners can detect significantly shorter BIACs compared with elderlies, and younger listeners can detect BIAC at significantly longer interaural delays (Li et al., 2009). When the noise arriving at one ear is delayed relative to that at the other ear, elderlies can not detect the BIAC as readily as younger adults, suggesting that elderlies have worse sound's waveform (mainly TFS) storage capacity, which indicates that the representation of aspects of the sound's waveform decays more rapidly in elderlies compared with younger listeners. Moreover, these age-related deficits are not associated with listeners' audiograms in previous studies (Li et al., 2009). In the present study, there was no significant correlation between PTA and BIAC delay threshold in the normal group, which was consistent with the previous studies. However, there was a substantial correlation between PTA (0.125–1 kHz) and BIAC delay threshold in the tinnitus group, suggesting the importance of identifying subjects' tinnitus in auditory research, especially in studies on the influence of aging.

Studies have investigated the sensitivity to binaural TFS changes across the older age range. The TFS-AF scores for elderlies are significantly poorer compared with young adults, which are decreased by about 162 Hz on average for each

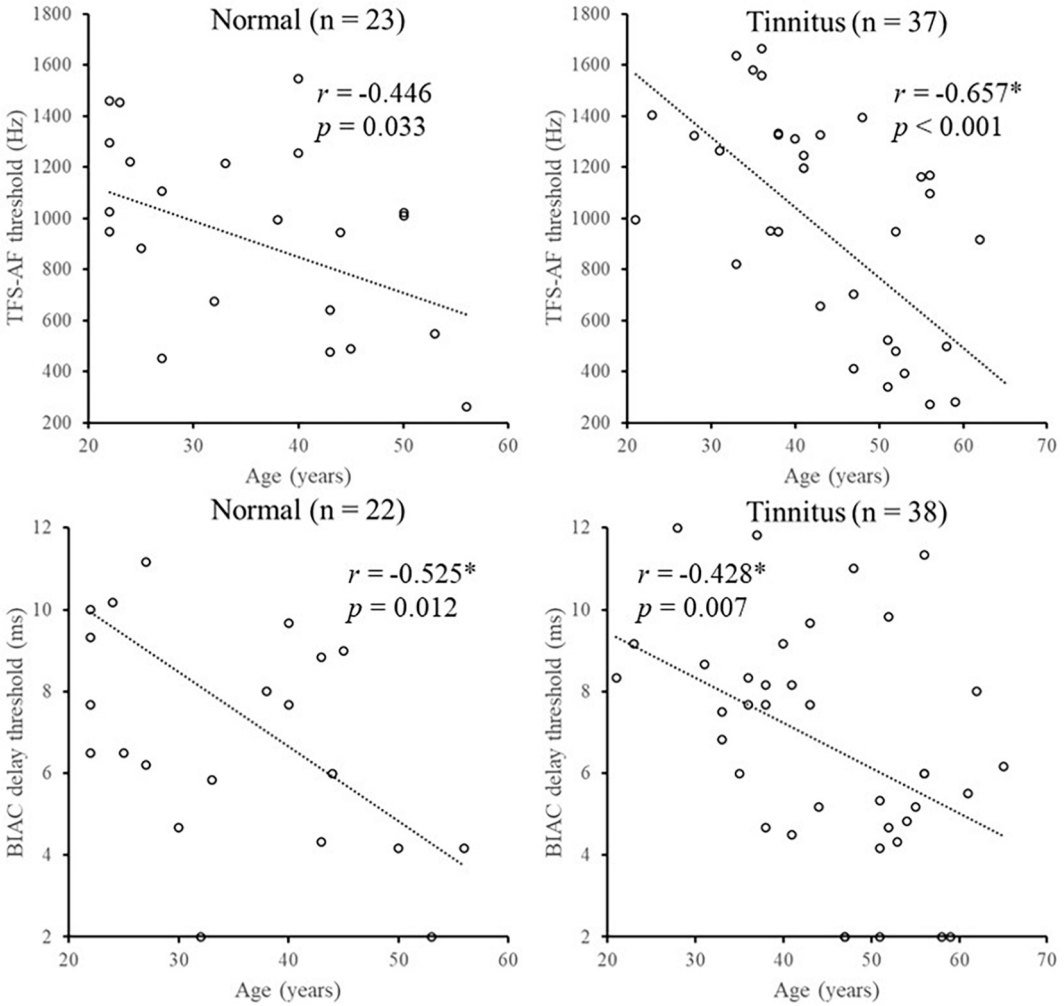

FIGURE 3 | Illustration of the correlation analysis of the BIAC delay threshold and TFS-AF test with age. *Significant effect after Bonferroni's correction, $p < 0.013$.

10-year increase in age over the range from 60 to 85 years (Füllgrabe et al., 2018). In the present study, we found that TFS-AF scores were associated with the BIAC delay threshold in the tinnitus group and also associated with UHF hearing thresholds (10–20 kHz). However, the variability and relationship of these indicators are different in different populations. Further details of the participants can be identified as much as possible in future research.

Performance on binaural tests, such as the BIAC delay threshold test and TFS-AF test, may depend partly on the monaural coding of TFS information before binaural interaction (Füllgrabe et al., 2017; Whiteford et al., 2017). Loss of inner hair cells can lead to more "noisy" TFS, which may be an age-dependent change that affects the processing of monaural TFS information (before the point in the auditory pathway where binaural interaction occurs) (Makary et al., 2011; Sergeyenko et al., 2013; Füllgrabe et al., 2018). On average, each inner hair cell and 3 to 4 outer hair cells form an acoustic frequency unit. Some studies suggest that tinnitus can be attributed to damage to the outer hair cells of the cochlea (Sztuka et al., 2010), and the occurrence of tinnitus with normal hearing may be an early signal of hearing loss and early damage of cochlear hair cells. Collectively, damage to hair cells might be one of the possible explanations of some correlation results in this study.

Several recent studies have proposed theoretical models based on stochastic resonances, which argue that adding neuronal internal noise to the system can counteract hidden and/or non-hidden hearing loss, and the development of a tinnitus percept is a side effect of this process (Krauss et al., 2016, 2018; Krauss and Tziridis, 2021; Schilling et al., 2021). Stochastic resonance models can explain some of the results of this study. In this study, hearing threshold and age showed a lower correlation in the tinnitus group, which may be the benefit of internal noise (Gollnast et al., 2017). To a certain extent, the BIC delay threshold reflects the ability to process the correlation (Li et al., 2013), and in the stochastic resonance model, auto-correlation of the sensor output is crucial for finding the optimal noise level that maximizes the mutual information between sensor input

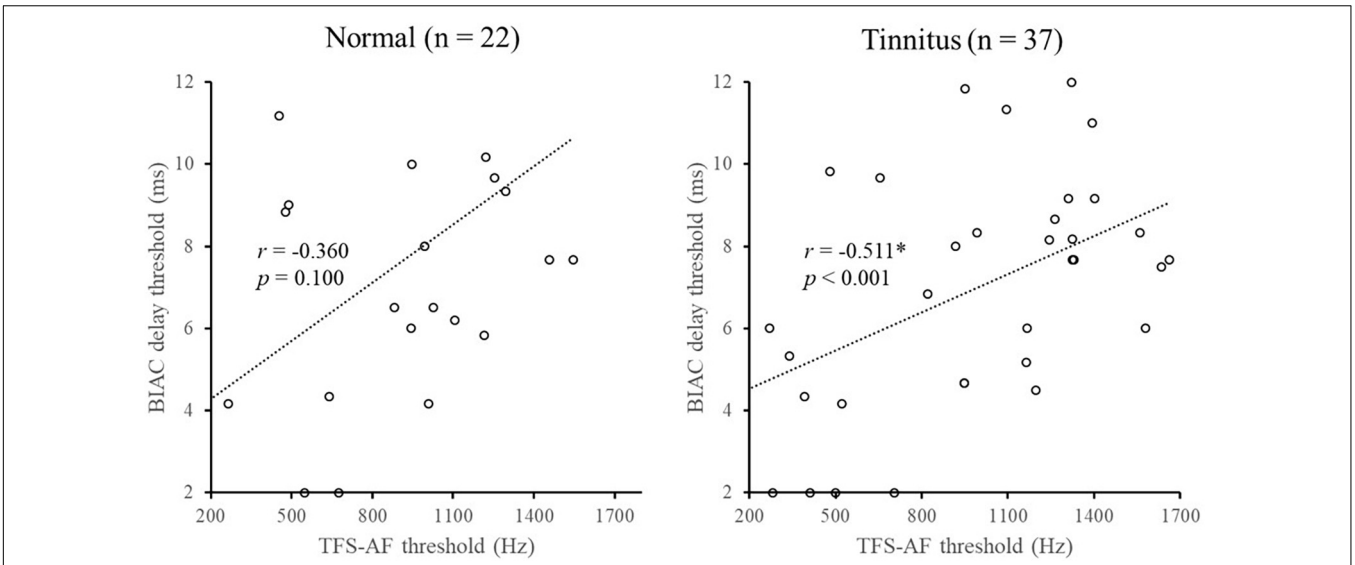

FIGURE 4 | Illustration of the correlation analysis of the BIAC delay threshold and TFS-AF test. *Significant effect after Bonferroni's correction, $p < 0.025$.

TABLE 1 | Spearman's r (with associated two-tailed significance levels in parentheses) between individual TFS-AF thresholds, BIAC delay thresholds, and UHF hearing thresholds for the normal group ($n = 37$) and tinnitus group ($n = 22$).

		$PTA_{0.125-1\ kHz}$	$PTA_{2-8\ kHz}$	$PTA_{10-20\ kHz}$
normal	BIAC delay threshold (ms)	−0.237 (0.288)	−0.174 (0.440)	−0.403 (0.063)
	TFS-AF threshold (Hz)	−0.335 (0.118)	−0.048 (0.830)	−0.301 (0.163)
tinnitus	BIAC delay threshold (ms)	−0.455 *(0.004)	−0.094 (0.574)	−0.323 (0.048)
	TFS-AF threshold (Hz)	−0.381 (0.020)	−0.286 (0.087)	−0.476* (0.003)

*PTA, pure-tone averages. *Significant effect after Bonferroni's correction, $p < 0.004$.*

and output (Krauss et al., 2017). Future studies can explore these models and mechanisms to explain potential relationships between these auditory indicators.

Limitations

The pathogenesis of tinnitus is complex, many factors can affect the occurrence of tinnitus, and different types of tinnitus may have different damage mechanisms. Due to the insufficient number of participants, further distinguishing the types of tinnitus would lead to insufficient testing power. Therefore, we could not conduct a more detailed discussion of the mechanism. The number of participants should be increased in future studies to further differentiate the types of tinnitus.

Some older participants (especially in the tinnitus group) had very poor test scores. Although they were able to complete the practice sessions and the early stages of the tests, the final results were very poor. Therefore, the analysis of the correlation was inevitably affected by extreme values. Although we used non-parametric tests (Spearman correlation analysis) to reduce the influence of extreme values, there was still a large part of the variability that could not be well explained. Future research will further refine the influencing factors and expand the number of participants to reduce this variability. This study presented all data points in scatter plots for reference.

CONCLUSION

In the present study, we examined the age-dependent changes of three types of auditory indicators, including TFS-AF thresholds, BIAC delay thresholds, and UHF hearing thresholds, in the normal group and tinnitus group. Among them, TFS-AF thresholds and BIAC delay thresholds had no significant difference between the two groups, while their relationship with age was more obvious in the tinnitus group. TFS-AF thresholds and BIAC delay thresholds reflect sensitivity and transient storage capacity of TFS, respectively, and the scores of these two tests were only significantly correlated in the tinnitus group. Correlations between UHF hearing thresholds and TFS-AF thresholds were observed only in the tinnitus group. Overall, the above results suggested that the influencing factors, such as tinnitus, should be fully considered when examining age-related hearing ability decline because the hearing ability of the tinnitus group might have greater variability and more obvious degradation.

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 human participants were reviewed and approved by the Tsinghua University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YD and MH: conception, design, acquisition of data, analysis of data, interpretation of data, writing – original draft, writing, review, and editing. YL: conception, design, data acquisition, data analysis, data interpretation, writing, review, and editing. CC: conception, design, funding acquisition, writing, review, and editing. YZ: data acquisition, data analysis, data interpretation, writing, review, and editing. All authors contributed to the article and approved the submitted version.

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Neural Plasticity Induced by Hearing Aid Use

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Age-related hearing loss is one of the most prevalent health conditions in older adults. Although hearing aid technology has advanced dramatically, a large percentage of older adults do not use hearing aids. This untreated hearing loss may accelerate declines in cognitive and neural function and dramatically affect the quality of life. Our previous findings have shown that the use of hearing aids improves cortical and cognitive function and offsets subcortical physiological decline. The current study tested the time course of neural adaptation to hearing aids over the course of 6 months and aimed to determine whether early measures of cortical processing predict the capacity for neural plasticity. Seventeen (9 females) older adults (mean age = 75 years) with age-related hearing loss with no history of hearing aid use were fit with bilateral hearing aids and tested in six testing sessions. Neural changes were observed as early as 2 weeks following the initial fitting of hearing aids. Increases in N1 amplitudes were observed as early as 2 weeks following the hearing aid fitting, whereas changes in P2 amplitudes were not observed until 12 weeks of hearing aid use. The findings suggest that increased audibility through hearing aids may facilitate rapid increases in cortical detection, but a longer time period of exposure to amplified sound may be required to integrate features of the signal and form auditory object representations. The results also showed a relationship between neural responses in earlier sessions and the change predicted after 6 months of the use of hearing aids. This study demonstrates rapid cortical adaptation to increased auditory input. Knowledge of the time course of neural adaptation may aid audiologists in counseling their patients, especially those who are struggling to adjust to amplification. A future comparison of a control group with no use of hearing aids that undergoes the same testing sessions as the study's group will validate these findings.

Keywords: age-related hearing loss, auditory processing, amplification, cortical auditory evoked potentials, plasticity, hearing aids, older adults

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INTRODUCTION

Aging can lead to sensory impairments such as age-related hearing loss, which is one of the most common sensory deficits in older adults (Vos et al., 2015; James et al., 2017; Haile et al., 2021). The global burden study (Haile et al., 2021) anticipates that by the year 2050, 698 million people will have moderate-to-profound hearing loss that could benefit from rehabilitation services, and approximately 66% of older adults aged 70 years or older will be reported to have bilateral hearing

loss (Collins, 1997; Bowl and Dawson, 2019). This age-related hearing loss may accelerate declines in cognitive and neural function and dramatically affect the quality of life (Heine and Browning, 2002; Lin et al., 2013; Loughrey et al., 2018; Rutherford et al., 2018); indicating a strong need for effective intervention.

Hearing aids are the most common treatment for mild-to-moderate age-related hearing loss. Although hearing aid technology has advanced dramatically over the last decade, the Global Burden of Disease estimates suggest that there is an 83% unmet need for hearing aids globally, calculated as the proportion of individuals with moderate-to-severe hearing loss who do not use a hearing aid (Orji et al., 2020). Our previous findings have shown that the use of hearing aids improves cortical and cognitive function (Karawani et al., 2018a) and offsets subcortical physiological decline (Karawani et al., 2018b). However, many people do not use their hearing aids (e.g., Bisgaard and Ruf, 2017; Hoppe and Hesse, 2017; Johnson et al., 2018), and one of the reasons for their lack of use is that they have difficulty adjusting to amplified sounds (Johnson et al., 2018). A better understanding of the hearing aid adjustment process and the time course of adaptation may lead to more effective management of hearing loss.

New hearing aid users require time to become accustomed to their hearing aids (e.g., Cox and Alexander, 1992; Gatehouse, 1992; Horwitz and Turner, 1997; Kuk et al., 2003; Munro and Lutman, 2003; Yund and Woods, 2010; Giroud et al., 2017; Karah and Karawani, 2022). Evidence supporting auditory adaptation with hearing aids is mixed, and the extent to which the auditory system adapts to new input remains unknown. The current study aims to test the time course of this adjustment period and to determine how objective measures can be used to provide information regarding potential hearing aid outcomes that can be used in the adaptation period. These aims will be accomplished by examining neuroplastic changes over the course of 6 months in newly fit hearing aid users.

Several studies have examined perceptual adaptation in older adults who were first-time hearing aids users, but they have had differing conclusions. Some studies show significant improvement in perceptual measures over time (Gatehouse, 1992; Horwitz and Turner, 1997; Munro and Lutman, 2003; Reber and Kompis, 2005; Munro, 2008; Olson et al., 2013; Lavie et al., 2015; Dawes and Munro, 2017; Karawani et al., 2018b; Karah and Karawani, 2022). For example, Gatehouse (1992) and Munro and Lutman (2003) tested older adult participants with sensorineural hearing loss who were fit with hearing aids monaurally. Following a period of 12 weeks of monaural hearing aid use in four participants, Gatehouse reported that aided speech recognition improved in the fitted ear but not in the unfitted ear. Munro and Lutman (2003) also observed significant improvements in speech recognition for the fitted vs. unfitted ears in sixteen participants. Reber and Kompis (2005) tested older adults who were fit with bilateral hearing aids at 2 weeks and 6 months after hearing aid use and found improvement in speech-in-noise recognition over time. Lavie et al. (2015) tested older adults after 4, 8, and 14 weeks of hearing aid use and found that unaided dichotic listening scores and unaided speech identification in noise improved significantly after 8 weeks of hearing aid use. Recently, Wright and Gagné (2020) showed an increase in speech in noise performance following 4 weeks of hearing aid use, suggesting an adaptation effect.

While these studies have suggested that adaptation may be observed post-fitting from four to eighteen weeks up to 6 months (e.g., Cox and Alexander, 1992; Gatehouse, 1993; Reber and Kompis, 2005; Giroud et al., 2017; Wright and Gagné, 2020), other studies reported that the effects were minimal (Bender et al., 1993), or not evident at all (Humes and Wilson, 2003; Dawes et al., 2014a). This inconsistency between studies may have been due to design and methodology factors, such as unilateral vs. bilateral fitting, the amount of auditory input and the period of the hearing aid use, and other hearing loss severity and cognitive factors (Palmer et al., 1998) or the timing of the baseline test. For example, Humes and Wilson (2003) tracked speech recognition changes over a 3-year period of bilateral hearing aid use in nine older adults at intervals of 1, 6, 12, 24, and 36 months after hearing aid fitting, and little evidence of speech recognition improvement in aided performance was noted. The initial testing of aided performance was conducted after 1 month of hearing aid use, and any possible gains in performance during the first month (e.g., Dawes and Munro, 2017; Wright and Gagné, 2020) may have limited the potential for further gains. Therefore, the current study aimed to examine effects of hearing aid use by controlling baseline measures on the day of fitting.

In addition to perceptual and behavioral measures, research has been conducted to study neural changes induced by newly fit hearing aids in older adults using subcortical (Philibert et al., 2005; Karawani et al., 2018b) and cortical (McCullagh, 2009; Dawes et al., 2014b; Giroud et al., 2017; Rao et al., 2017; Habicht et al., 2018; Karawani et al., 2018a; Maruthy, 2019; Glick and Sharma, 2020) electrophysiological measures. Other research has been conducted in experienced users (e.g., Gatehouse, 1995; Munro et al., 2007; Bertoli et al., 2011; McClannahan et al., 2019). In the following paragraphs, we focus on previous studies that have evaluated changes in cortical auditory evoked potentials (CAEPs) in new hearing aid users.

The CAEP has been used to examine the effects of auditory stimulation and amplification while wearing hearing aids in normal-hearing and hearing-impaired participants (e.g., Korczak et al., 2005; Billings et al., 2007, 2011; Van Dun et al., 2016; Jenkins et al., 2018). More specific to the current study, CAEPs have been used to examine neural changes in hearing ability following a period of hearing aid use (McCullagh, 2009; Dawes et al., 2014b; Giroud et al., 2017; Rao et al., 2017; Karawani et al., 2018a; Habicht et al., 2018; Maruthy, 2019). CAEPs have relatively high temporal resolution and can provide detailed insights into the neural processing of auditory signals and integrative processing in the auditory cortices (for a review, see Eggermont, 2007).

As mentioned earlier, a number of studies have tracked the results of using bilateral newly fit hearing aids using CAEPs for a period of 4 weeks to 6 months in older adults. Specifically, Rao et al. (2017) studied P3 peak changes using an oddball paradigm to assess neural changes after 4 weeks of hearing aid use and found a significant reduction in P3a amplitude. Giroud et al. (2017) also used an active oddball paradigm, and reported significant reductions in the global field power in the P3b after

3 months of intensive hearing aid use. Habicht et al. (2018) combined electrophysiology (N2 and P3 responses) and eye tracking to compare newly fit hearing aid users with experienced users. The first-time hearing aid users group showed smaller N2 amplitudes than the experienced users at baseline; however, no changes in N2 amplitudes were observed over time (after 24 weeks in the first-time hearing aid group). McCullagh (2009) observed earlier N1 latencies after 6–8 weeks of hearing aid use but did not observe changes in N1 and P2 amplitudes or P2 latency. They suggested that the change observed in N1 latency reflects a physiological adaptation effect.

Karawani et al. (2018a) compared a group of first-time hearing aid users with a hearing-matched control group with no use of hearing aids after a period of 6 months. The use of hearing aids was associated with improvement in working memory performance and increased cortical response amplitudes for the N1 and P2 peaks. The N1 component is believed to reflect early triggering of attention to auditory signals (Näätänen, 1990; Čeponien et al., 2002). Therefore, this finding suggests that increased auditory experience gained through hearing aid use for 24 weeks resulted in greater allocation of attentional resources to the signal. The P2 peak component is believed to reflect auditory object identification (Ross et al., 2013), and changes in P2 amplitudes were positively related to working memory improvement. These amplitude enhancements suggest that hearing aid use may alter cortical processing and reflect a physiological adaptation effect. These results contrast with those of Dawes et al. (2014b) who did not report changes in cortical amplitudes/latencies after hearing aid use, possibly due to differences in stimuli. Dawes et al. (2014b) presented pure-tone stimuli through insert earphones while Karawani et al. (2018a) presented speech stimuli through free-field speakers. Stimulus type might affect the neural encoding in the central auditory system (Tremblay et al., 2004; Billings et al., 2011; Xie et al., 2021), and the P1-N1-P2 complex is sensitive to stimulus characteristics (e.g., Papanicolaou et al., 1984; Ostroff et al., 2003; Michalewski et al., 2005).

Our previous study (Karawani et al., 2018a) showed changes in neural processing after 6 months of hearing aid use. In the current study, we aimed to determine the time course of the changes in CAEP amplitudes noted in that previous study (N1 in quiet, P2 in quiet, and P2 in noise) at six time points: 0, 2, 6, 12, 18, and 24 weeks of hearing aid use. We also aimed to determine if these measures can be used by the clinician to provide information regarding potential adaptation to newly fit hearing aid individuals. We should note that that a control group was tested during the first and last sessions, but the study lacked a control group that underwent testing during the other four sessions.

MATERIALS AND METHODS

Participants

Data from thirty-one older adults (18 females) between the ages of 60–84 years were included in this study. These data were taken from a larger research study (previously published in Karawani et al., 2018a,b) from the Washington D.C. metro area. All participants were native English speakers recruited through printed advertisements in local senior living communities and Craigslist advertisements. The Institutional Review Board of the University of Maryland, College Park approved all procedures. All participants provided written, informed consent prior to participation and received compensation for their time. Participants underwent bilateral audiometric threshold assessment of pure-tone air-conduction (from 250 to 8,000 Hz) and bone-conduction (from 250 to 4,000 Hz) thresholds. They had sensorineural symmetrical hearing loss with no air-bone gaps or asymmetries between ears exceeding 15 dB HL. All participants underwent cognitive evaluation using the Wechsler Abbreviated Scale of Intelligence (Zhu and Garcia, 1999) and had normal IQs ($\geq$85). The Montreal Cognitive Assessment (MoCA) was used to screen for mild cognitive impairment (Nasreddine et al., 2005), a cutoff of 22/26 was used as suggested by Dupuis et al. (2015) for individuals with hearing loss. Participants had no history of neurological or psychiatric diseases, were native English speakers (with no report of bilingualism), and had no significant history of musical training.

Participants that met the inclusion criteria listed above were fit with bilateral hearing aids and were seen in several testing sessions during a period of 6 months. The final number of participants that completed all six sessions and were included in the experimental group of the current study was 17 (9 females, mean age = 75 years $\pm$ 6); their audiograms are shown in **Figure 1**.

Study Design

All participants in the experimental group were fit with bilateral hearing aids and tested in six testing sessions as shown in **Figure 2**. Hearing aids were fit at the first session, and the participants returned for follow-up testing at 2, 6, 12, 18, and 24-week intervals. Electrophysiological testing was conducted at each session.

Data from a control group who underwent identical testing sessions in sessions one and six were used in the analysis to ensure that there were no cortical changes between these sessions. These control data from the first and sixth sessions were published in Karawani et al. (2018a). The control group consisted of 14 participants (9 females; mean age 74 $\pm$ 6) and were fit with bilateral hearing aids during the two testing sessions, but they did not use any hearing aids through the period between sessions one and six. The control group serves as a comparable group to the experimental group in these demographic factors (presented in **Table 1**): age, gender, pure-tone average hearing and high-frequency hearing, IQ, and MoCA scores; $p > 0.08$. The control group's data analysis showed that there was no cortical change in amplitudes of the peaks P1, N1, and P2 between sessions 1 and 6 in quiet [P1: $t(13) = 0.236$, $p = 0.816$; N1: $t(13) = 1.102$, $p = 0.290$; P2: $t(13) = 0.238$, $p = 0.816$] or in noise [P1: $t(13) = 0.769$, $p = 0.455$; N1: $t(13) = 0.527$, $p = 0.607$; P2: $t(13) = 0.425$, $p = 0.678$]. In addition, there was no significant change in latencies of the peaks P1, N1, and P2 between sessions 1 and 6 in quiet [P1: $t(13) = 0.265$, $p = 0.795$; N1: $t(13) = 0.676$, $p = 0.511$; P2: $t(13) = 1.940$, $p = 0.075$] or in noise [P1: $t(13) = 1.946$, $p = 0.074$; N1: $t(13) = 0.689$, $p = 0.503$; P2: $t(13) = 0.123$, $p = 0.240$]. There were no significant

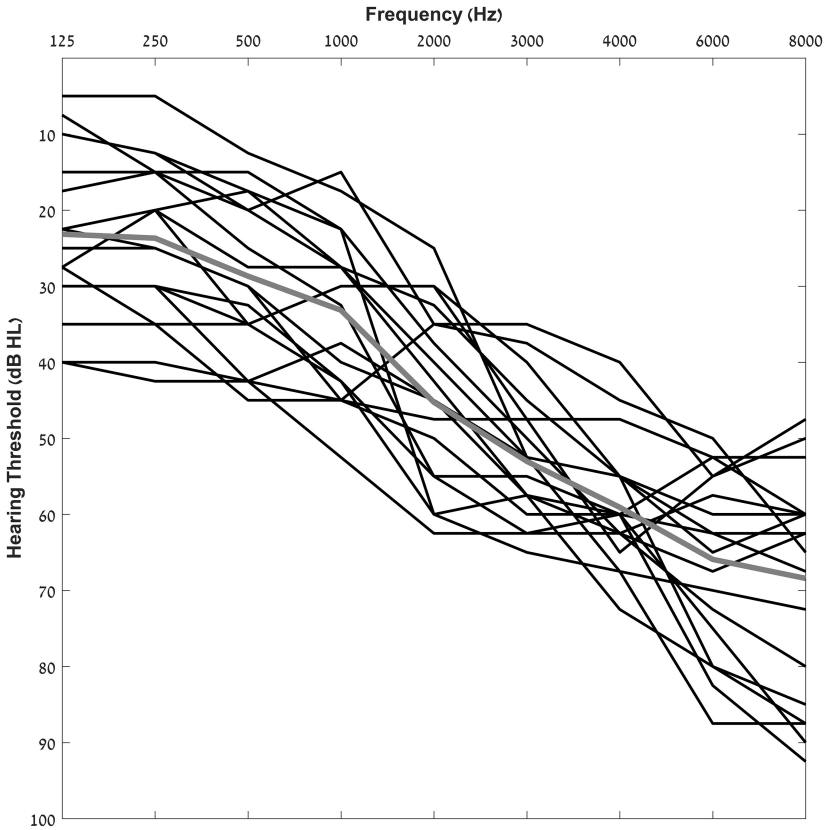

FIGURE 1 | Individual pure-tone air-conduction thresholds for participants from 125 to 8,000 Hz. The solid gray line indicates group average pure tone thresholds.

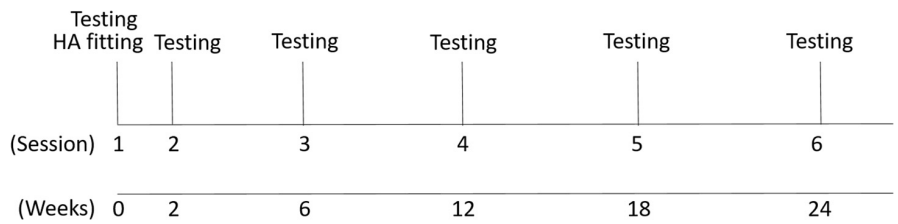

FIGURE 2 | Study design. Six testing sessions were conducted. The first session included the hearing aid fitting and EEG recording and the second to sixth sessions (EEG recording and hearing aid checks of data logging) were conducted after the hearing aid fitting in time intervals shown in weeks.

differences between the control and the experimental group in session 1 in any of the cortical components across conditions [$t(29) < 1.087$, $p > 0.285$] (**Figure 3**). The sections below refer to the analysis conducted for the seventeen participants in the experimental group.

Hearing Aid Fitting

The hearing aid fitting procedure was previously described in Karawani et al. (2018a). Receiver-in-the-canal Widex Dream 440 hearing aids were used for bilateral fitting. The hearing aids had size M receivers (to ensure accommodation to hearing losses up to 85 dB HL from 125 to 8,000 Hz) and domes most appropriate for their hearing loss, (open: thresholds for 250–500 Hz < 30 dB HL; tulip: individual thresholds for 250–500 Hz ≥ 30 dB HL). The hearing aid fitting was performed immediately following the audiologic examination on the first day of testing. For the purpose of this study, a single automatic program was used. In addition, the participants did not have the opportunity to alter the hearing aid gain. Real-ear measurements were performed to verify the fitting (for more details please refer to Karawani et al., 2018b). Most of the output values met the Goodness of Fit test ($F > 5.315$, $p < 0.030$, R-squared > 0.181). Maximum power output measurements were conducted to ensure that the hearing aids did not exceed maximum tolerance limits. On the first day, the participants received an in-service on hearing aid use and were instructed to begin wearing their hearing aids at least 8 h per day. Participants were advised that the hearing aids were set according to their audiometric thresholds, and that for

TABLE 1 | Demographics.

	Experimental	Control	*t*(29)	*P*-value
N	17	14		
Age range (years)	60–84	62–84		
Age (years)	75.41 (6.71)	73.71 (5.79)	0.739	0.466
Male/female	8/9	5/9	1.036	0.309
Pure-tone average hearing (0.5–4 kHz; dB HL)	42.20 (7.18)	40.21 (8.37)	0.713	0.482
High-frequency hearing (6–8 kHz; dB HL)	65.58 (11.54)	60.98 (13.47)	1.026	0.314
IQ	114.05 (9.32)	112.72 (6.94)	1.673	0.120
MOCA	26.88 (1.69)	25.24 (2.45)	1.811	0.088

Groups were matched on all demographic factors. Means (SDs) are displayed for age, sex distribution, hearing, IQ, and Montreal Cognitive Assessment (MoCA) scores. Number of participants in each group (N), t-values with degrees of freedom and P-values of the group comparison are also shown.

the purposes of the study aims, no changes could be made to the settings. They were also told that they would adjust to the prescribed amplification if they wore their hearing aids on a daily basis. Upon request, at the end of 6 months, changes were made to features such as gain, amplification, directionality, etc. To ensure compliance, monitoring of hearing aid use (average hours/day) was done at each follow-up session through the hearing aid data logging function available through the Widex software platform (group average = 9.31 h/day ± 2 h).

Cortical Auditory Evoked Potentials

All tests were conducted in an electrically-shielded sound-attenuated booth. Participants wore their hearing aids during the recording session and were seated in an upright position at a distance of two meters from an Interacoustics SP90 speaker at 0° azimuth (as described in Karawani et al., 2018a,b). This seating position was identical in all testing sessions. During the recordings, participants watched a silent, closed-captioned movie of their choice to facilitate a relaxed but wakeful state. Cortical auditory-evoked potentials (CAEPs) were recorded to a 170-ms speech syllable/ga/presented through the Interacoustics speaker via Presentation software (Neurobehavioral Systems, Inc.) in two listening conditions: (1) 80 dB SPL in quiet (referred to as quiet condition) and (2) 80 dB SPL in the presence of 70 dB SPL 6-talker babble [+ 10 dB Signal-to-noise ratio (SNR), noise condition]. The 6-talker babble was taken from the Words-in-Noise sentence lists (Wilson et al., 2003) and was continually looped every 4.6 s. For more specific details of stimulus features, please refer to Karawani et al. (2018a). A Larson Davis System 824 sound level meter was used to perform calibration prior to each session to ensure that the /ga/and noise stimuli were within ± 1 dB of the stimulus level at ear level.

Recording

The Biosemi Active-Two acquisition system (BioSemi B.V., Amsterdam, Netherlands) was used to record responses at a sampling frequency of 2,048 Hz via a 32-channel electrode cap. The offsets for all channels were below 50 μV, and earlobes served as references. Six hundred artifact-free sweeps were collected for each condition.

Data Processing and Analyses

MATLAB (MathWorks, version R2011b) was used for offline processing. Zero-phase offline bandpass filtering was performed from 1 to 30 Hz, using a 4th-order Butterworth filter. An electro-oculography reduction method (Romero et al., 2006; Schlögl et al., 2007) was used to remove eye movements. Each sweep consisted of a time window of −100 to 400 ms with respect to the stimulus onset. The offline artifact-reject criterion was set at ± 100 μV. The final average response was composed of the first 500 artifact-free sweeps.

Data Analysis

Karawani et al. (2018a) found significant amplitude increases for N1 in quiet and for P2 in quiet and in noise; therefore, in the current manuscript, we limited our analyses to these components. An automated peak-peaking algorithm in MATLAB was used to calculate mean response amplitudes from the Cz electrode for the expected time regions of each of the dominant cortical peaks: N1 (80–150 ms) and P2 (160–250 ms) in the quiet condition, and N1 (150–200 ms) and P2 (225–275 ms) in the noise condition. The test-retest reliability of the CAEP amplitudes is moderate relative to brainstem amplitudes (Bidelman et al., 2018). Because we wanted to maximize test-retest reliability, we chose to measure changes in the Cz amplitude, which is more robust in quiet and noise (Papesh et al., 2015).

Statistical Analysis

Changes across six sessions: Repeated measures analyses of variance (RMANOVA) were performed using time (6 sessions) as a within-subject factor for amplitude and latency of peaks N1 (in quiet and in noise) and P2 (in quiet and in noise), followed by planned paired *t*-tests. *Predictive measures*: As stated in the introduction, we also aimed to determine if these amplitude measures can be used by the clinician to provide information regarding potential adaptation to newly fit hearing aid individuals. Therefore, regression model analysis was conducted to determine whether earlier sessions predicted improvement in the final session. *Confidence intervals* (Lambert et al., 1991): We calculated the confidence intervals for amplitudes across participants at session 1, and then used this measure as a criterion to determine the presence of singificant amplitude changes in individual participants at each follow-up session.

RESULTS

Changes Across Six Sessions

The RMANOVA showed a main effect of time [$F_{(5,\ 16)} = 2.055$, $p = 0.006$, $\eta^2_p = 0.128$]. *Post hoc* pairwise comparisons between sessions after adjusting for multiple comparisons (Benjamini and Hochberg, 1995) showed that changes from session 1 were observed earlier for N1 amplitude than those for P2 amplitude,

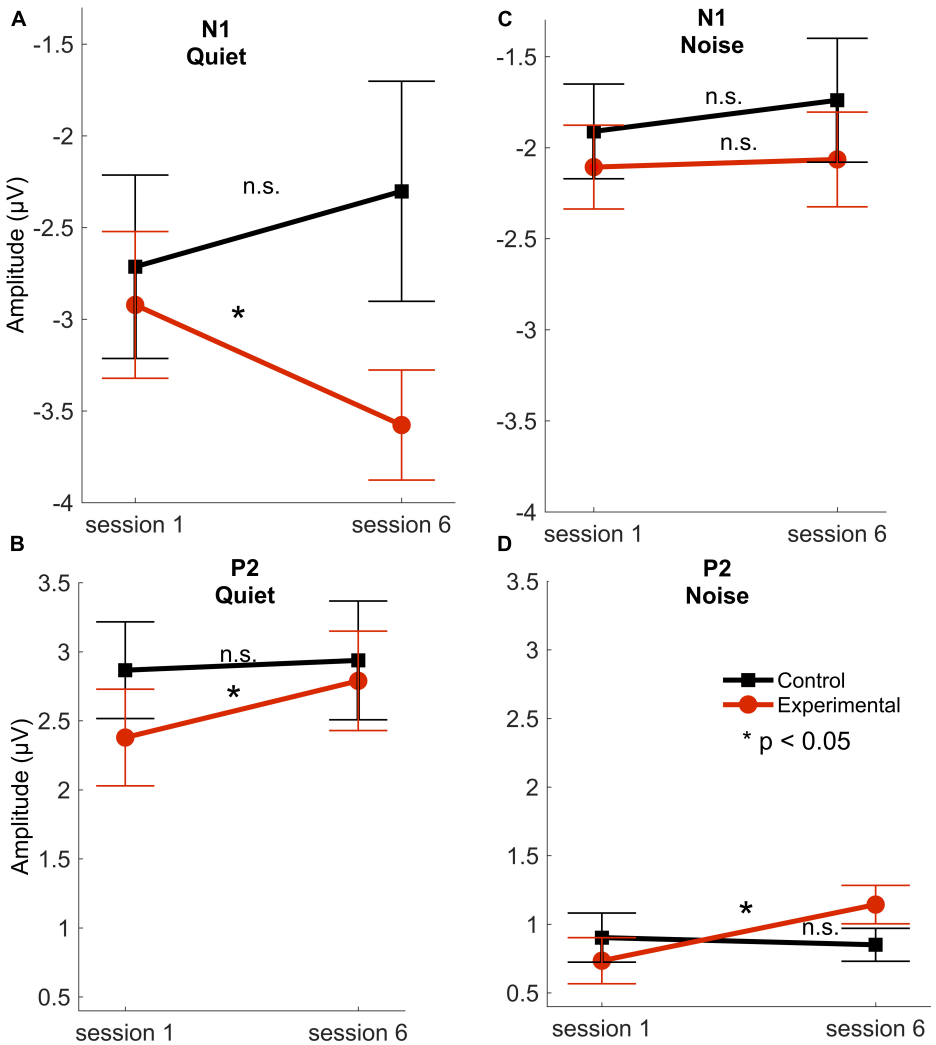

FIGURE 3 | Response amplitudes. N1 and P2 mean amplitudes for the experimental (red circles) and control (black squares) groups across sessions 1 (first) and 6 (last) in quiet **(A,B)** and noise **(C,D)** conditions. Error bars represent standard error of the mean. *$P < 0.05$. n.s, not significant. There were no significant differences between the control and experimental groups in session 1 in any of the cortical amplitudes in quiet [N1: $t(29) = 0.665$, $p = 0.511$; P2: $t(29) = 1.331$, $p = 0.194$] or in noise [N1: $t(29) = 0.597$, $p = 0.555$; P2: $t(29) = 0.505$, $p = 0.617$] (modified with permission from Karawani et al., 2018a).

such that N1 amplitude in quiet increased as early as 2 weeks after the hearing aid fitting ($p = 0.031$), but P2 amplitude in quiet did not increase until 6 weeks after hearing aid fitting ($p = 0.033$). Furthermore, a significant increase in P2 amplitudes in noise was observed in the final session—24 weeks following the initial hearing aid visit ($p = 0.012$) (**Figures 4**, **5**), but N1 in noise amplitudes did not show any significant changes ($p > 0.3$). Taken together, these results demonstrate evidence of neuroplasticity in N1 amplitudes earlier (2 weeks following hearing aid fitting) than P2 amplitude changes (6 weeks after hearing aid fitting). The time course of neuroplasticity during the period of hearing aid use is reflected in **Figure 5**. For each participant, amplitude values were adjusted such that session 1 (day 1) values were fixed to 0, then, for each subsequent session, amplitude values were presented as the difference (in μV) from session 1. The RMANOVA was also conducted on the peak latency values and no main effect of time was observed [$F_{(5, 16)} = 1.156$, $p = 0.334$], consistent with our previous finding of no change in latency between sessions 1 and 6.

Predictive Measures

We tested whether changes in N1 amplitude that were observed in the earlier sessions predicted the increase in amplitude in the final session (week 24), thus providing a prognosis for eventual hearing aid improvement. Therefore, we examined the amplitude of N1 in quiet at the first session along with the change in amplitude in session 2 and session 3; i.e., 2, and 4 weeks after fitting, to determine whether clinicians can use these measures in these early sessions to provide the patient with expectations regarding the adaptation process. The "Enter" method of linear regression was used since it specifies the order of variables in the model, and the

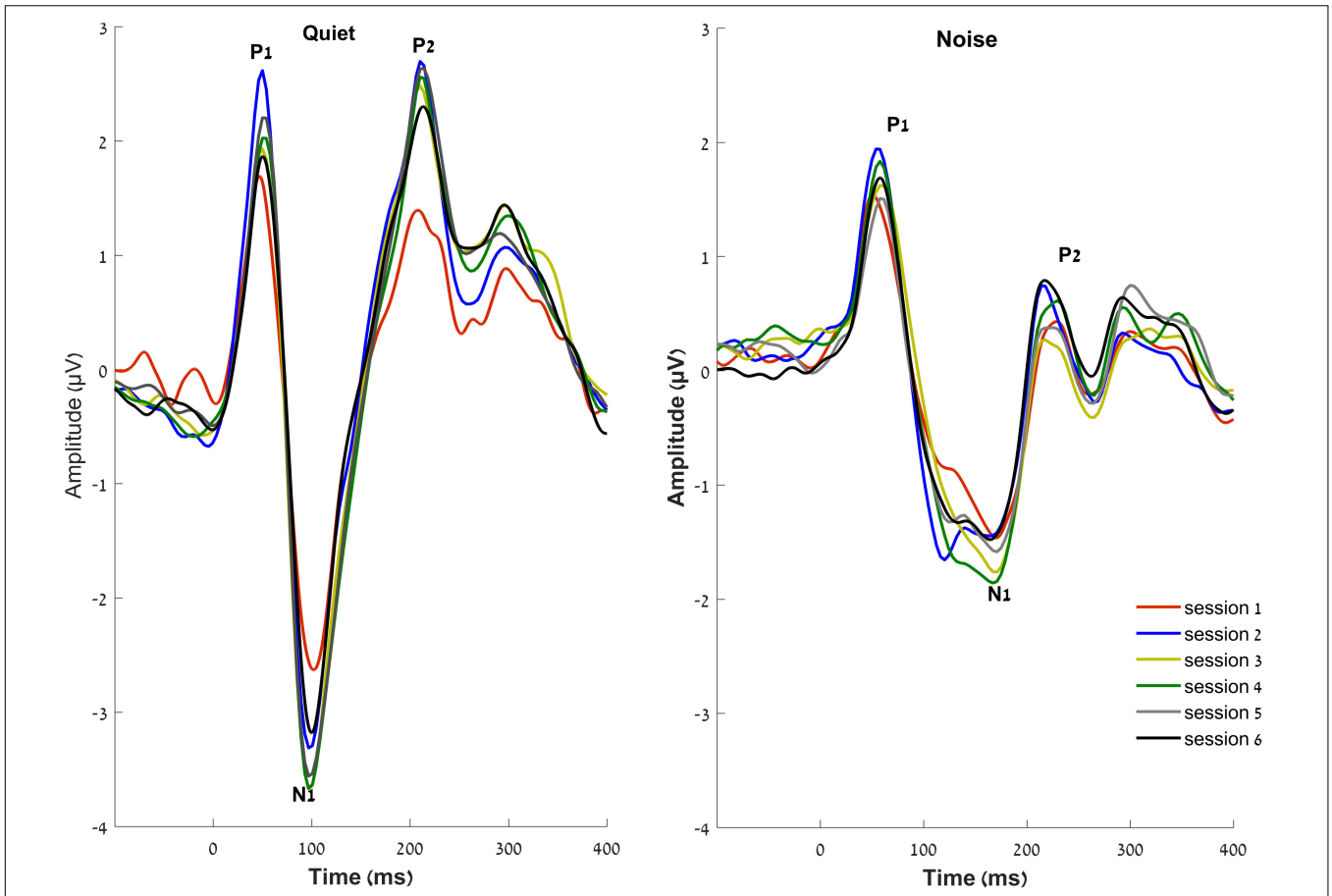

FIGURE 4 | Grand averaged waveforms of the experimental group at the vertex electrode Cz, in quiet **(right)** and noise **(left)** conditions over the six sessions.

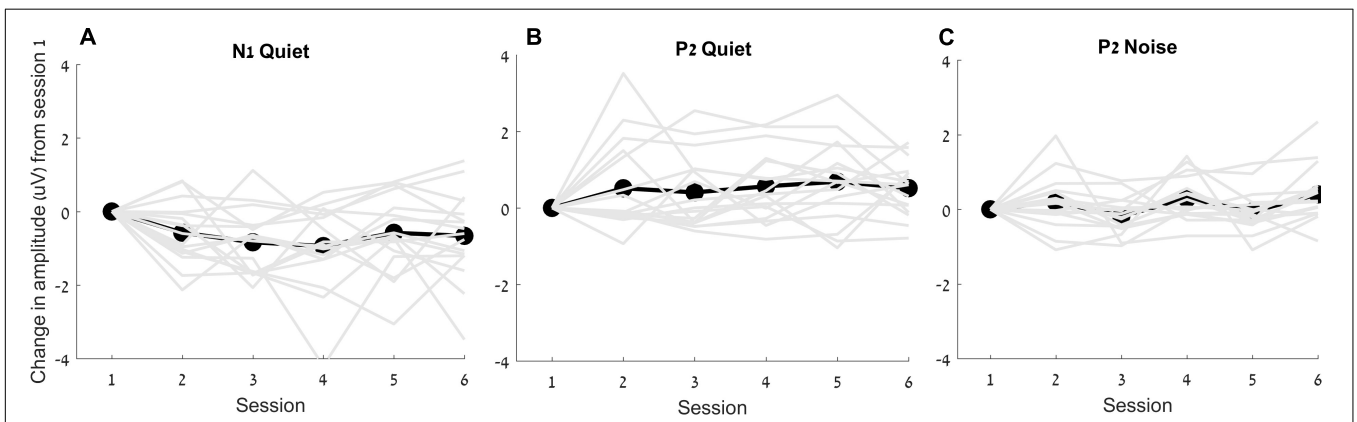

FIGURE 5 | Change in amplitudes (in μV) from the first session for N1 in quiet **(A)**, P2 in quiet **(B)** and P2 in noise **(C)** are plotted for each individual (gray lines) as well as for the average (black lines).

independent variables were entered in the following order: amplitudes at session 1, change in amplitude at session 2 and change in amplitude at session 3, with change in amplitude at session 6 as the dependent variable. To rule out strong correlations between predictor variables, collinearity diagnostics were performed showing satisfactory variance inflation factor (highest = 1.30) and tolerance (lowest = 0.76) scores. The analysis showed that the earlier sessions highly predict variance in the sixth session ($R^2 = 0.655$, $p = 0.004$) (**Table 2**). Of the three measures, the amplitude change at session 3 was the only variable that significantly predicted change at session 6 ($p = 0.01$).

Confidence Intervals

The 85% confidence intervals were calculated for session 1 across measures to determine the criterion for significant amplitude change in an individual (see **Table 3**). This percentage was chosen rather than the conventional 95% confidence interval due to our relatively small sample size and preliminary nature of the study (Lee et al., 2014). For N1 amplitudes in quiet the criterion for significant change was 0.61 μV, for P2 amplitude in quiet the criterion was 0.50 μV, and for P2 amplitude in noise the criterion was 0.25 μV. The results show that for N1 amplitude in quiet, 47% of the participants demonstrated a significant increase after 2 weeks (i.e., 47% had a change larger than 0.61 μV) and 64% demonstrated a significant increase after 6 weeks (**Table 4**). For P2 amplitude in quiet, 50% of the participants demonstrated a significant increase after 12 weeks, and for P2 amplitude in noise, improvement in 50% of more of the participants was not observed until 24 weeks of the use of hearing aids.

DISCUSSION

The main goal of the present study was to determine the time course of neural adaptation to hearing aids and to determine whether early measures of cortical processing predict the capacity for neural change. The current study tested neuroplastic changes induced by hearing aid use over the course of 6 months using CAEPs. Neural changes were observed as early as 2 weeks following the initial fitting of hearing aids. The results showed a neural relationship between responses in earlier sessions and the change predicted after 6 months of the use of hearing aids. These results are significant, because a period of 4 weeks is usually provided for adjustment to the hearing aids, during which the patient can decide whether or not to keep the hearing aids, and knowledge of the potential for neural adaptation may be useful in the decision making process.

A previous study by the authors (Karawani et al., 2018a) reported significant improvements in CAEPs following 24 weeks of hearing aid use. The current study suggests that increases in N1 amplitude can be observed as early as 2 weeks following hearing aid fitting, whereas P2 amplitudes appear to require a longer time course of 6 weeks to observe similar amplitude increases. In the following paragraphs, we discuss a possible interpretation of this finding by considering the generators and mechanisms of both components.

P2 appears to reflect stimulus detection and identification, based on the spectral information provided by temporal-lobe generators, specifically located in auditory cortices of Heschl's gyrus (e.g., Lütkenhöner and Steinsträter, 1998). N1 generators were shown to provide sound feature specifics and serve the pre-attentive detection of auditory events (Näätänen, 1990). Therefore, N1 might contribute to the processing of word onsets (e.g., Eggermont and Ponton, 2002) and phonetic structure (e.g., Sanders and Neville, 2003) during the perception of continuous speech, and reflects sensitivity to sound audibility (Martin et al., 1997) and early triggering of focused attention to the incoming auditory stimuli (Čeponienė et al., 2008). P2 generators might have access to more fine-grained spectral stimulus information than the N1 generators (Čeponienė et al., 2008), and therefore P2 peak has been shown to reflect integration of stimulus features to facilitate auditory object representation and stimulus identification (Näätänen and Winkler, 1999; Čeponienė et al., 2008; Ross et al., 2013). This level of resolution was reflected in the findings of the current study. It appears that stimulus detection improves rapidly (N1 amplitude changes) after increased audibility through hearing aid use, but a longer period of adaptation to hearing aids is required for identification and assignment of relevance of the stimulus (reflected by P2). Therefore, increased audibility through hearing aids may facilitate rapid increases in cortical detection, but a longer time period of exposure to amplified sound may be required to integrate features of the signal and form auditory object representations.

TABLE 2 | Regression model: Early sessions predicted neuroplastic changes after 6 months of hearing aid use.

	R	R_{change}^2	F_{change}	df1,df2	*p*
Model	0.809	0.655	7.589	3,13	0.004
Variables				β	
Amplitude (session 1)				0.192	0.34
Change in amplitude (session 2–session 1)				0.362	0.05
Change in amplitude (session 3–session 1)				0.576	0.01

R for full model and the change in R-squared and statistics (following the addition of the change in the later sessions), F-values with degrees of freedom and p-values are presented. Standardized (β) coefficients and significance (p-values) in each variable's contribution to the model is also presented for the N1 amplitudes collected in sessions 1, the change in N1 amplitude observed in sessions 2 and session 3.

TABLE 3 | Confidence interval of the difference.

Session 1	85% Confidence interval of the difference		
	Lower	Upper	Difference from the mean (μV)
N1 in quiet	−3.77	−2.53	0.61
P1 in quiet	1.71	2.72	0.50
P2 in noise	0.489	0.99	0.25

Values presented for session 1 across the three components: N1 in quiet, P2 in quiet and in noise.

TABLE 4 | Percentage of the individuals that met the clinical criteria of improvement.

	Session 2	Session 3	Session 4	Session 5	Session 6
N1 in quiet	47%	65%	59%	53%	48%
P1 in quiet	35%	41%	41%	62%	56%
P2 in noise	41%	24%	47%	18%	53%

We note that significant increases in P2 amplitudes were observed only after session 4. Therefore, it is less likely that P2 amplitudes were affected by increased stimulus exposure or repeat testing effects, at least in the early weeks of the study, as has been reported in previous auditory training studies in normal-hearing young adults (Tremblay et al., 2010, 2014). Based on these studies, we might have expected to find P2 but not N1 changes at the second and third follow-up visits. We believe that the differences in findings may arise from differences in hearing ability between groups. Perhaps older adults with hearing loss require more experience with audible sound to show changes in cortical processing. Therefore, the changes we found for the P2 component in older adults with hearing loss may be a potential indicator of later adaptation to hearing aids, as discussed above.

As mentioned in the introduction, studies have shown mixed results concerning neural adaptation at subcortical (e.g., Philibert et al., 2005; Habicht et al., 2018) and cortical levels (e.g., Billings et al., 2007; Bertoli et al., 2011; Dawes et al., 2014b; Dawes and Munro, 2017; Giroud et al., 2017; Karawani et al., 2018a). The current study demonstrates rapid neural adaptation to hearing aids using CAEPs in older adults. Giroud et al. (2017) also reported changes in brain activity after the use of hearing aids for 12 weeks. Maruthy (2019) also showed evidence for neural plasticity and hearing aid benefits after 1 month of hearing aid use, using methods similar to those in the present study (CAEPs) but in younger to middle-aged adults (ages 23–60 year). They reported earlier P1 and N1 latencies after 4 and 8 weeks following the initial fitting of hearing aids. Other research has also documented neural adaptation using other electrophysiological measures. A recent study using cortical visual evoked potentials reported that after hearing aid use for a period of 6 months, reduced cortical activation in temporal and frontal regions with increased activation in visual regions were observed for visual stimuli processing (compared to baseline non-hearing aid use), suggesting neural plastic changes in the cortex after the use of hearing aids for 6 months (Glick and Sharma, 2020). Using Functional magnetic resonance imaging (fMRI), Yu et al. (2017) reported neural changes assessed by fMRI in a clinical case study. An older adult with bilateral sensorineural hearing loss was fit for the first time with hearing aids and was tested at baseline and after 8 weeks. After 8 weeks of hearing aid use, increased responses to audio-visual stimulation was observed, specifically in the superior temporal sulcus (STS). They suggest that this increased activation seen in the STS following the use of hearing aids reflects increased phonological representation of speech sounds, and more efficient use of auditory cues due to adaptation to acoustic amplification through hearing aids. Taken together, rapid neural adaptation can be assessed as soon as 2–4 weeks following hearing aid fitting. The combination of electrophysiological and imaging paradigms would be important for further investigation of neuroplastic changes induced by hearing aids.

CONCLUSION

Age-related hearing loss is considered one of the most prevalent health conditions in older adults (Yueh et al., 2003). Although hearing aid technology has advanced dramatically over the last decade, less than one quarter of the population of older adults with hearing loss use hearing aids (Popelka et al., 1998; Lin, 2011). This untreated hearing loss may accelerate declines in cognitive (Lin, 2011; Lin et al., 2013; Peelle and Wingfield, 2016) and neural function (Karawani et al., 2018a). The finding of the current study that cortical changes may occur in as little as 2 weeks may provide encouragement regarding the potential for neuroplasticity, and perhaps eventual improvements in perception. Perhaps this knowledge may increase the patient's willingness to persist with the process of adaptation.

LIMITATIONS

This study was a relatively small study with the aim of providing pilot data for a larger study that includes more participants and a longer adaptation period. Therefore, a larger cohort would be needed to overcome inter individual variability. Due to the limited nature of the study, it was only possible to test the control group at sessions 1 and 6. Therefore, the observed changes in the hearing aid use group may be due to repeated testing effects. Future studies should include a control group that is tested for the same number of sessions, or perhaps a delayed treatment group that includes multiple baselines. Another suggestion for future research is to conduct a similar study design with first time hearing aid users but with a parallel group of experienced users, and for a longer period of auditory rehabilitation. In addition, associating the neural findings with behavioral changes in speech perception is important, and a future study would benefit from the inclusion of perceptual/self-assessment measures at all-time points. Finally, a future study should consider employing an active listening protocol to eliminate possible confounds of watching a subtitled movie on attention-related cortical components.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the University of Maryland, College Park. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HK designed the study, analyzed the data, interpreted the results, and wrote the manuscript. KJ collected the data. SA designed the study, collected the data, interpreted the results, and wrote the manuscript. All authors approved the final version of the manuscript.

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REVIEW
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A Review of ApoE4 Interference Targeting Mitophagy Molecular Pathways for Alzheimer's Disease

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Alzheimer's disease (AD) is one of the major worldwide causes of dementia that is characterized by irreversible decline in learning, memory loss, and behavioral impairments. Mitophagy is selective autophagy through the clearance of aberrant mitochondria, specifically for degradation to maintain energy generation and neuronal and synaptic function in the brain. Accumulating evidence shows that defective mitophagy is believed to be as one of the early and prominent features in AD pathogenesis and has drawn attention in the recent few years. *APOE* ε4 allele is the greatest genetic determinant for AD and is widely reported to mediate detrimental effects on mitochondria function and mitophagic process. Given the continuity of the physiological process, this review takes the mitochondrial dynamic and mitophagic core events into consideration, which highlights the current knowledge about the molecular alterations from an *APOE*-genotype perspective, synthesizes ApoE4-associated regulations, and the cross-talk between these signaling, along with the focuses on general autophagic process and several pivotal processes of mitophagy, including mitochondrial dynamic (DRP1, MFN-1), mitophagic induction (PINK1, Parkin). These may shed new light on the link between ApoE4 and AD and provide novel insights for promising mitophagy-targeted therapeutic strategies for AD.

Keywords: Alzheimer's disease, mitophagy, mitochondrial dynamics, apolipoprotein E, neurodegenerative disease

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INTRODUCTION

Alzheimer's disease (AD) is the most common and well-known form of dementia and features age-related and progressive recognition impairment, memory loss, and learning failure, accompanied by encephalatrophy, and extracellular amyloid-β (Aβ) plaques, intracellular tangles of hyperphosphorylated Tau (Mahaman et al., 2022). Since the global aged tendency of the population has a dramatic impact on an individual and family development, and social healthcare costs throughout the world, AD with widespread prevalence has become an increasingly challenging task for elderly care, public health, and all the human beings (2020 Alzheimer's disease facts and figures, 2020). Therefore, AD targets or therapeutical strategies are urgent to be proposed currently.

It is extensively recognized that the apolipoprotein E4 (*APOE* ε4) allele remains the strongest genetic risk for sporadic AD (Belloy et al., 2020; Serrano-Pozo et al., 2021). *APOE* ε4 allele, usually existing in approximately 15% of people, lowers the age of AD onset and increases the risk of AD in a dose-dependent manner (Levy et al., 1990; Wallon et al., 2012; Ward et al., 2012; Tang et al., 2016). Accumulating difficulties remain when Aβ-targeting interference fails to effectively halt or slow clinical AD progression (Bohrmann et al., 2012; Salloway et al., 2014; Bomasang-Layno and Bronsther, 2021; Pleen and Townley, 2022); thus, it is widely believed that amyloid cascading seems to appear as less possibility for a major explanation of AD pathogenesis. Other rising insights draw more and more interests broadly. The existing investigation of *APOE* ε4 pathogenesis in AD (Norwitz et al., 2021; Serrano-Pozo et al., 2021) has expanded beyond Aβ peptide-centric mechanisms to Tau neurofibrillary degeneration, neuroinflammation (Kaur et al., 2019; Leng and Edison, 2021), synaptic loss (Zhao et al., 2020), depression (Rhodes et al., 2021; Zhang et al., 2021), blood–brain barrier disruption (Rhea and Banks, 2021; Zhang and Xie, 2021), insulin resistance (Jabeen et al., 2021), gut dysfunction (Hoffman et al., 2019), oxidative stress (Butterfield and Mattson, 2020), and autophagic deficit (Chen et al., 2021; Sohn et al., 2021; Eran and Ronit, 2022); particularly, damaged mitophagy (Simonovitch et al., 2019; Schmukler et al., 2020; Liang et al., 2021a; Morton et al., 2021; Wang et al., 2021b). However, the precise molecular mechanisms underlying ApoE4 pathogenic effects during AD have not yet been elucidated.

Mitochondria consisting of the outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM), intermembrane space, and mitochondrial matrix performs diverse essential roles in multiple intracellular homeostasis events, including tricarboxylic acid cycle, β-oxidation of fatty acids, genetic information storage, Ca^{2+} homeostasis, and biosynthesis of intermediates for cell growth or death (Moreira et al., 2010; Kauppila et al., 2017). The integrity of the mitochondrial structure is indispensable for mitochondrial function and mitophagy, which demonstrates major involvement in Aβ and Tau pathology (Parker et al., 1994; Zhu et al., 2013; Monzio Compagnoni et al., 2020). Diverse mitophagy-dependent signaling pathways have been established, many of which are conserved from *Caenorhabditis elegans* to humans (Egan et al., 2011; Fivenson et al., 2017; Kerr et al., 2017; Gustafsson and Dorn, 2019; Cai and Jeong, 2020; Wang et al., 2021b). Mitophagy, a stress-response mechanism to suppress mitochondrion-dependent apoptosis for neuronal protection (Pan et al., 2021), is fairly fundamental for mitochondrial quality control, function recovery, and self-renewal, whose deficiency is revealed in AD iPSC-derived neurons, as well as hippocampal samples from the AD model mice and patients with AD, thus receiving growing attention as a promising mechanism for AD-targeted therapy of late years (Fang et al., 2014, 2019; Xu et al., 2017; Tran and Reddy, 2020; Sukhorukov et al., 2021; Wang et al., 2021b). Specifically, accumulating evidence implies that mitophagy deficit fails to maintain mitochondrial clearance (Kerr et al., 2017), axonal transport (Ashrafi and Schwarz, 2015), and synapse biosynthesis (Pan et al., 2021), which exacerbates neuroinflammation, Aβ and p-Tau deposition, and energy dysfunction, thereby promoting AD pathology and memory loss (Song et al., 2021). Mitophagy-dependent signaling is reported to not only reduce Aβ and tau pathology (Pan et al., 2021), but also alleviate cognitive damages (Fang et al., 2019; Pan et al., 2021) through AMPK and SIRT1 activation, mTOR inhibition, and lysosomal functional improvement in AD progression (Fang et al., 2019). These evidence suggest that normal mitophagy protection or maintenance is an essential target for AD therapeutic development, while there is yet no effective and clear therapeutic approach by which to artificially manipulate mitophagy so as to improve the clinical symptoms and prolong the survival of patients affected by AD. Given its significance in various physiological processes, mitophagy has been barged to the forefront of AD researches after being studied for years. ApoE isoforms have been reported to have multiple effects of mitochondrial dysfunction, and mitophagy and ApoE4 seem to have negative impacts on diverse physiological processes (Chang et al., 2005; Chen et al., 2011; Orr et al., 2019; Horner et al., 2020; Schmukler et al., 2020; Yin et al., 2020; Liang et al., 2021b; Qi et al., 2021; Eran and Ronit, 2022). Many issues remain ambiguous and seem appealling for further investigations, however, both the functional and mechanistic multiformity of ApoE4 effects of mitophagy have emerged and been extensively enlightened in AD pathogenesis (Chen et al., 2011; Palikaras et al., 2017; Simonovitch et al., 2019; Schmukler et al., 2020; Sohn et al., 2021; Eran and Ronit, 2022).

Here, we have reviewed emerging findings for the central and multi-faceted roles that mitophagy plays in the pathogenesis of AD, described physiological changes from the pre-mitophagy events to mitophagy proceeding considering the continuity of the physiological processes, integrated the signaling pathways suggesting the relationships between ApoE4 and mitophagy deficit, and discussed the underlying mechanisms that how ApoE4 triggers these abnormalities and ultimately contributes to AD pathogenesis, while highlighting potential therapeutic targets that may correct these dysfunctions (**Figure 1**).

APOE4 AND GENERAL AUTOPHAGIC PROCESSES IN AD

Autophagy is a ubiquitous event highly conserved from yeast to mammals and functions as a recycling system for maintaining metabolic homeostasis and cellular self-renewal (Parzych and Klionsky, 2014). Strictly, there are four main forms—macroautophagy, microautophagy, chaperone-mediated autophagy, and selective autophagy. The term "autophagy" usually means "macroautophagy", a non-selective process. In autophagy, cargoes are labeled and enclosed by a double-membrane vesicle and become autophagosomes, then autophagosomes recruit and fuse with the lysosome to address degradation. Namely, this is highly dependent on functionally vesicular trafficking (Parzych and Klionsky, 2014). Relatively, selective autophagy is when several specific organelles, such as mitochondria, lipids, and endoplasmic reticulum (ER), fulfill their degradation by the core machinery of autophagy (Scrivo

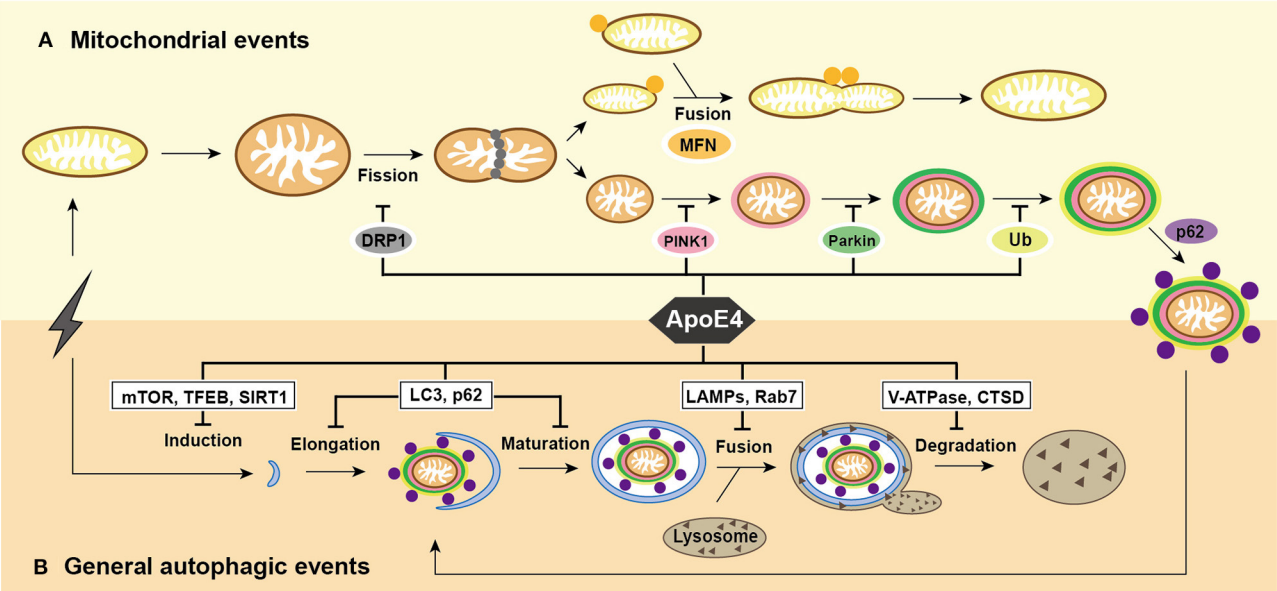

FIGURE 1 | Summary of mitochondrial events and general autophagic events under ApoE4 intervention. **(A)** After excessive cellular stress, mitochondria begin to swell and fragment into healthy mitochondria for fusion, and pre-degraded mitochondria for mitophagy. damaged mitochondria induce PINK1/Parkin pathways and then participate in general autophagic flux. ApoE4 is directly or indirectly involved in mitochondrial events, including DRP1 pathways during fission; the MFNs pathways during fusion; and the PINK1/Parkin pathways during mitophagic induction. **(B)** After excessive cellular stress, the omegasome is initiated to form an elongated into a phagophore, which encloses the damaged mitochondria and becomes a mature autophagosome. Lysosomes recruit to autophagosome and fuse with it to form autolysosome, the ultimate area of mitochondrial degradation. ApoE4 intervenes autophagic initiation by the mTOR, TFEB, and SIRT1 pathways; compromises elongation by LC3, p62, and Rab5 pathways; blocks autophagosome-lysosome fusion by the Rab7, LAMP2, and LAMP1 pathways; damages lysosomal degradation by CTSD and V-ATPase pathway.

et al., 2018). Mitophagy is a selective mode of autophagy targeted engulfment and destruction of mitochondria, namely, mitophagy shares several common mechanisms with autophagy.

Autophagy mediates the degradation of abnormal cellular components or damaged organelles, closely associated with ontogeny and growth, oxidative damage protection, the malignant proliferation of tumor cells, and neurodegenerative diseases (Parzych and Klionsky, 2014). It is extensively believed autophagic impairment in AD and *APOE* genotypes plays diverse roles in the underlying mechanisms (Chen et al., 2021). Specifically, ApoE4 mainly inhibits autophagic initiation by the upregulation of the mammalian target of rapamycin (mTOR), the binding to transcription factor EB (TFEB), the inhibited expression of Surtuin 1 (SIRT1), and forkhead box O3a (FOXO3a), and their signaling pathways, respectively (Theendakara et al., 2016; Parcon et al., 2018; Lima et al., 2020; Sohn et al., 2021); thereby interfering with phagophore elongation and completion, which is involving PI3K, LC3, p62, and Rab5 (Gilat-Frenkel et al., 2014; Ong et al., 2014; Simonovitch et al., 2016; Nuriel et al., 2017; Parcon et al., 2018; Li et al., 2019), blocking autophagosome-lysosome fusion by lysosomal associated membrane protein 1 (LAMP1), LAMP2, and Rab7-dependent movement (Nuriel et al., 2017; Parcon et al., 2018) and damages phospholipid homeostasis and lysosome membrane integrity (Ji et al., 2002; Zhu et al., 2015; Persson et al., 2017). This compromises lysosomal degradation by the leakage of cathepsin D (Ji et al., 2002; Belinson et al., 2008; Nuriel et al., 2017; Persson et al., 2017) and the abnormal lysosomal acidification mediated by the proton pump V-ATPase (Nuriel et al., 2017; Larramona-Arcas et al., 2020). As a part of these general processes of autophagy—initiation, elongation, autophagosome-lysosome fusion, and lysosomal degradation—overlapped with those of mitophagy and they share common mechanisms, namely, it is probably that ApoE4 also impedes mitophagy by these common processes.

We have summarized ApoE4 regulation on the stages shared by mitophagy and autophagy and illustrated the insights underlying AD-targeted therapy, then we will discuss the association between ApoE4 and mitophagy from the perspective of mitophagy-exclusive processes, including mitochondrial dynamic equilibrium (fission and fusion), and mitophagy-specific induction.

APOE4 AND MITOPHAGY-SPECIFIC PROCESSES IN AD

Mitochondria is a highly dynamic organelle that can form long tubular networks for highly interconnected networks, and continually undergoes the cycle of fusion and fission in response to environmental changes (Wolf et al., 2020). When mitochondria are damaged, the swelling mitochondria

trigger component redistribution and are divided into relatively healthy mitochondria for fusion and damaged mitochondria for mitophagy and degradation. After fission events, depolarized mitochondria induce PTEN-induced putative kinase 1 (PINK1)/Parkin-dependent mitophagy (Wolf et al., 2020; Luan et al., 2021). As mitochondrial events are closely linked and occur in succession, mitochondrial fission and fusion are disrupted followed by aberrant mitophagy.

ApoE4 and Mitochondrial Fission in AD

Mitochondrial fission is required for mitophagy and mitochondrial transport, while fusion prevents mitochondria from undergoing mitophagy by replenishing mitochondrial DNA and promoting biolipid exchange (Wolf et al., 2020). Mitochondria fission is a basic and vital process *via* programmed and sequential membrane movement that (Mahaman et al., 2022) involves healthy mitochondria fragments for growing physiological requirements; (2020) aged or damaged mitochondria divided into healthy mitochondria for recycling and pre-degraded mitochondria for clearance (Wolf et al., 2020; Luan et al., 2021). Impaired mitochondrial dynamics is widely established in AD model mice and cells, as well as AD individuals (Manczak et al., 2011; Reddy et al., 2011, 2018; Manczak and Reddy, 2012a; Zhu et al., 2013; Kandimalla et al., 2021), as determined by the lower expression of mitochondrial fission genes (*DRP1* and *FIS1*) and higher phosphorylation level of dynamin-related protein1 (DRP1), leading to reductive mitochondria fragmentation and neuronal energy dysfunction (Reddy et al., 2011; Manczak and Reddy, 2012a; Misrani et al., 2021; Wang et al., 2021a; Dhapola et al., 2022). Incidentally, additional studies indicate that decreased DRP1 promotes cognitive performance and improves mitophagy and dendritic spines in tau-transgenic mouse model and APP/PS1 mice (Kandimalla et al., 2021; Misrani et al., 2021; Song et al., 2021), in which DRP1 is overactivated under abnormal conditions; and consistently, various DRP1 inhibitors promote fusion and improve cognition in AD (Dhapola et al., 2022). These suggest that correcting DRP1 activity might confer tolerance to cytotoxicity from p-Tau and Aβ (Manczak and Reddy, 2012a; Kuruva et al., 2017; Reddy and Oliver, 2019) and there is a need for further investigation into the identified regulation underlying AD events.

DRP1 GTPase and its receptors (FIS1, MFF, MID49, and MiD51/MIEF1) are the most broadly investigated fission regulators network in recent years (Chan, 2012). Mitochondrial fission is promoted by DRP1-Ser616 phosphorylation and inhibited by DRP1-Ser637 phosphorylation (Taguchi et al., 2007; Cereghetti et al., 2008; Chang and Blackstone, 2010). DRP1 translocation induces mitochondrial dynamics disturbance and contributes to the imbalance of mitochondrial dynamics toward fission, consequently triggering mitophagy and inhibiting pathogen-induced apoptosis (Schmukler et al., 2020). ApoE3 is the most common isoform found among people, thus usually functioning as the control group during ApoE4 studies (Liu et al., 2013). Compared to ApoE3, ApoE4 inhibits *DNM1L* transcription and attenuates DRP1 expression in astrocyte cell lines (Schmukler et al., 2020), primary astrocytes, and hippocampus from *ApoE*-TR mice (Yin et al., 2020), and the ostmortem brain specimens from *APOE* ε4 carriers and patients with AD carrying *APOE* ε4/4 (Simonovitch et al., 2019; Yin et al., 2020). DRP1 level is not different in ApoE3 and ApoE4 astrocytes with the treatment of lysosomal inhibitor chloroquine or proteasomal inhibitor MG-132, indicating that DRP1 lysosomal and proteasomal degradation pathways are not affected by *APOE* genotype (Schmukler et al., 2020). ApoE4 attenuates carbonyl cyanide m-chlorophenyl hydrazone (CCCP)-induced increase of DRP1 in ApoE4-astrocytes compared to ApoE3, indicating an impaired stress reaction to mitochondrial energy disorders (Schmukler et al., 2020). These results suggest that decreased DRP1 level may majorly result in compromised RNA synthesis induced by ApoE4 (**Figure 2**), instead of enhancing lysosomal and proteasomal degradation (Gomes et al., 2011; Rambold et al., 2011; Simonovitch et al., 2019; Schmukler et al., 2020). However, other studies display inconsistent observations. ApoE4 (Δ272–299), an effective fragment derived from ApoE4, promotes MFF expression and DRP1-Ser616 phosphorylation as well, and compromises mitofusin (MFN)−1 and−2 and optic atrophy 1 (OPA1) expression *in vitro*, indicating that ApoE4 (Δ272–299) possess pro-fission activation and fusion inhibition (Liang et al., 2021b). These contradictory observations probably are by virtue of the effects of different structural features. It is well-known that ApoE4 detrimental pathogenic effects are highly dependent on its peculiar conformation with a more compacted structure and higher oligomerized inclination, which is resulted from two amino acid residues varying from ApoE3 (Chen et al., 2011). Accordingly, ApoE4 is more susceptible to cleave than ApoE3 (Huang et al., 2001; Kothari et al., 2021). Different ApoE4 fragments differentially couple with certain neurotoxicity and induce mitochondrial disorders (Chang et al., 2005). Both the lipid-binding region (amino acids 241–272) and receptor-binding region (amino acids 135–150) are indispensable for ApoE4 neurotoxicity, and the amino acids 273-299 are identified for its neuroprotection (Chang et al., 2005). Only ApoE4 fragments with these two regions can escape from the secretory pathway and interact with mitochondria, thus impairing mitochondrial function and integrity (Chang et al., 2005). Briefly, in our views, concerning the comprehensive effects of integrated protein structure, full-length ApoE4, instead of its (Δ272–299) fragment, is proposed to play primary roles to inhibit fission by DRP1 expression, of course, there is still appealed for further investigation in the complicated potency and the prime functional regions. Incidentally, glucose-regulated protein 75 (GRP75) inhibitor is effective to correct the pro-fission activation induced by the ApoE4 (Δ272–299) (Liang et al., 2021b), indicating a promising insight for AD-targeted therapy.

Owing to a lack of detailed investigation into DRP1 properties, it is also worth determining the DRP1 activity changes from the ApoE4 perspective or evaluating mitochondrial fission from other perspectives. Although the regulatory effects of ApoE4 on fission have been established, the alternative mechanisms that how ApoE4 affects DRP1 function in addition to transcription remain unknown, and the potential signaling interactions are here summarized. First, ApoE4 exerts multiple inhibitions on SIRT1 dynamics and function (Theendakara

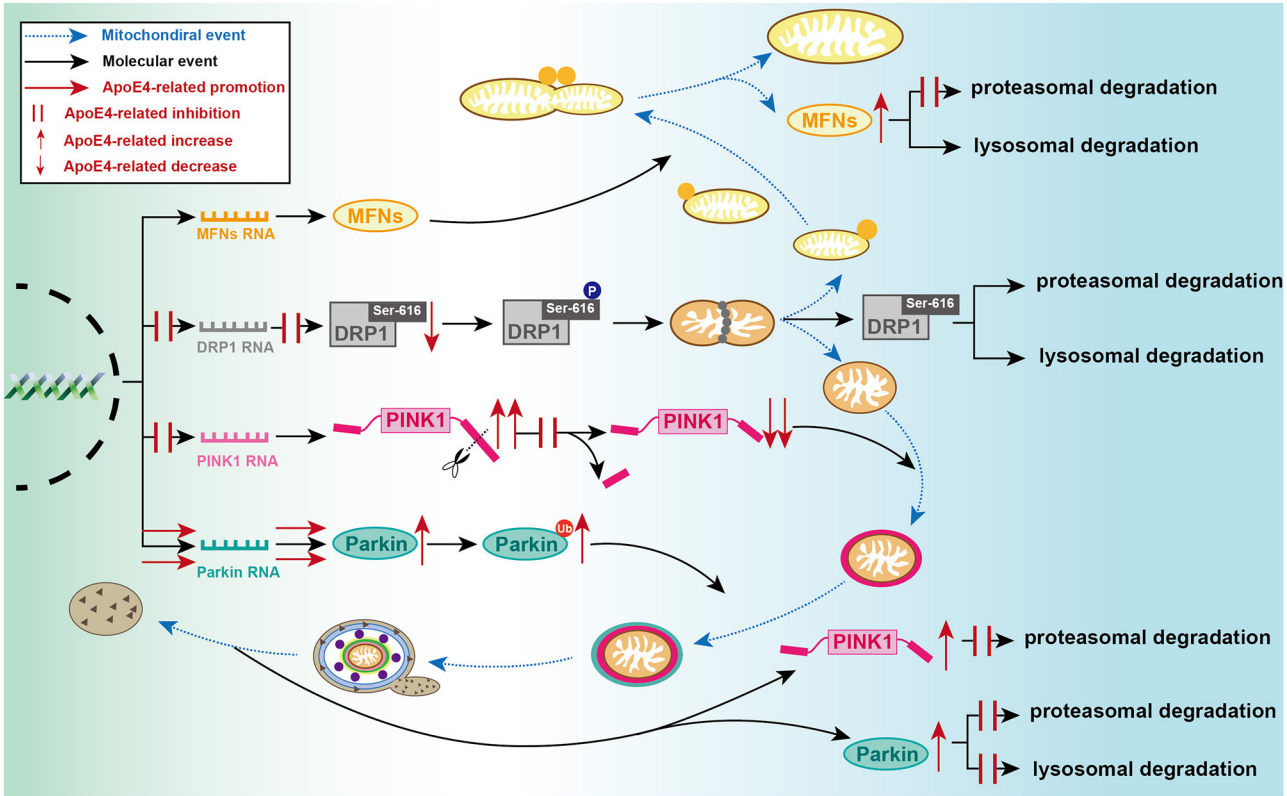

FIGURE 2 | Detailed processes of established ApoE4-mediated regulation of mitochondrial events at molecular level. During mitochondrial fusion, ApoE4 interferes with MFNs proteasomal degradation, then leading to MFN dynamic dysfunction. During mitochondrial fission, ApoE4 inhibits DRP1 transcription and expression, thus leading to a lower capacity of fission. During mitophagic induction, AcpoE4 inhibits PINK1 transcription and impairs proteolytic cleavage of FL-PINK1, exemplified by FL-PINK1 elevation and cleaved-PINK1 reduction. ApoE4 also blocks PINK1 proteasomal degradation, resulting in PINK1 dynamic dysfunction. ApoE4 not only promotes Parkin transcription and expression but also disrupts both proteasomal and lysosomal degradation, leading to a remarkable increase of ubiquitinated Parkin and total Parkin.

et al., 2013, 2016), then resulting in disturbance of SIRT1-mediated mitochondrial fragmentation in mitophagy (Qiao et al., 2018). Specifically, in both the *in vivo* and *in vitro*, ApoE4 interferes with *SIRT1* transcription, expression, and enzyme activity more than ApoE3 (Lattanzio et al., 2014; Theendakara et al., 2016) and the inhibited effects seem to result from a pretranscriptional affect—the specific binding of ApoE4-*SIRT1* promoter with the highest affinity among ApoE isoforms (Theendakara et al., 2016; Lima et al., 2020). Moreover, only ApoE4 triggers SIRT1 mislocalization to the cytoplasm and impairs the SIRT1 function (Theendakara et al., 2016; Lima et al., 2020). Notably, overexpressed SIRT1 can rescue ApoE4-induced physiopathologic alterations in AD events (Theendakara et al., 2013). Since SIRT1-involved neuroprotection plays extensive and multiple roles in AD progression (Fujita and Yamashita, 2018; Gomes et al., 2018), it might be helpful to extract the relationship between SIRT1 and ApoE4 and the potential mechanisms. Second, the abnormal interactions between DRP1 and hyperphosphorylated Tau, as well as DRP1 and Aβ monomers and oligomers, are established by coimmunoprecipitation (co-IP) and double-labeling immunofluorescence analysis, in postmortem brain tissues of AD patients and brain homogenates from several AD mouse models (Manczak et al., 2011; Reddy et al., 2011; Manczak and Reddy, 2012a; Abtahi et al., 2020; Kandimalla et al., 2021), which is speculated that excessive p-Tau and Aβ accumulation may synergistically disrupt mitochondrial fragmentation in a ApoE4-dose-dependent manner. These findings may help to shed new light on the alternative link between ApoE4 and mitophagic dynamics.

Taken together, these findings suggest that ApoE4 disrupts mitochondrial fission by the inhibition of DRP1 transcription and expression (Schmukler et al., 2020), DRP-Aβ interaction (Manczak et al., 2016), DRP1-Tau interaction (Kandimalla et al., 2016), and the downregulation of its regulators SIRT1 level (Theendakara et al., 2013), ultimately resulting in dysregulated mitochondrial dynamics, consequently probably triggering irreversible and progressive neuronal damage and cognitive impairment (Manczak and Reddy, 2012a). These seem to reveal a new hypothesis for neurodegeneration in AD involving mitochondrial dynamics and ApoE4-targeted pathology at the molecular level, leading to a better understanding of

the mechanisms underlying the ApoE4 regulatory effect on mitophagy in AD.

ApoE4 and Mitochondrial Fusion in AD

Mitochondrial fusion includes two types IMM fusion is facilitated by OPA1 and OMM fusion is majorly dependent on the oligomerization of MFN-1 and−2 (Eisner et al., 2018; Tilokani et al., 2018; Dhapola et al., 2022). MFN-1 and−2 are transmembrane GTPases embedded in OMM that are usually degraded by proteasomes to prevent mitochondrial fusion and maintain mitochondrial fission (Nguyen et al., 2016; Meng et al., 2019). Mitochondrial fusion is established associations with AD pathogenesis as determined by the mitochondrial dynamic proteins that influence AD cognitive function in a dose-dependent manner (Yin et al., 2020). Interestingly, some reports indicate increased levels of MFN-1, MFN-2 and OPA1 are detected in hippocampal tissue of patients with AD and APP/PS1 mice (Wang et al., 2009, 2021b; Song et al., 2021), while another study found decreased levels of mitochondrial fusion genes (*MFN-1*, *MFN-2*, *TOMM40,* and *OPA1*) in the frontal cortex tissue from AD patients (Reddy et al., 2011), which may be explained by the samples from different brain region and appeals for further investigation and reconfirmation in detail Although the definite alterations and impacts remain contradictory and ambiguous, at least, there are some associations between mitochondrial fusion and AD pathogenesis to a certain extent.

The mitochondrial network is hyperfused in ApoE4 astrocytes (Schmukler et al., 2020). ApoE4 elevates MFN-1 protein level in N_2a cells (Orr et al., 2019), astrocytes cell lines (Schmukler et al., 2020), primary astrocytes, and brain tissues from young 5-month-old *APOE* ε4-TR mice (Simonovitch et al., 2019). However, the expression of MFN-1 and MFN-2 have significantly decreased in the postmortem brain tissues of *APOE* ε4 carriers with a mean age of 84.6 years (Yin et al., 2020). The contradictory results may be involved in a discrepancy of different ages or objects. For instance, the MFN-1 level is decreased in AD patients with a mean age of 88.5 years (Yin et al., 2020), while the levels of MFN-1, MFN-2, and OPA1 are increased in the hippocampus of patients with AD with the age range from 60 to 89 years, in which the mean age is lower (Wang et al., 2009). Specifically, in young subjects, MFN production normally remains and is able to function compensatory in response to ApoE4-induced damage, thus majorly demonstrating degradation blockage exemplified by MFN elevation (Orr et al., 2019; Simonovitch et al., 2019; Schmukler et al., 2020). With increasing age, age possesses more profound and irreversible degenerated potency on overall cellular metabolisms (Mkrtchyan et al., 2020; Wissler Gerdes et al., 2020) and the compensatory capacity may have been exhausted. Thus, old subjects majorly demonstrate deficient production exemplified by MFN reduction. It may be helpful to study MFN-1 changes under the specific conditions, such as in *APOE* ε4/4/AD patients or animal models. Despite the inconsistent results, there are certain association between ApoE4 and mitochondrial fusion proteins. Additionally, compared to ApoE3 astrocytes, the increase of total MFN-1 and ubiquitinated MFN-1 are lower in APOE4 astrocytes without transcriptional change, while it is found the consistent alteration under MG-132 treatment (Schmukler et al., 2020). These results indicate ApoE4 induces MFN-1 accumulation and defective degradation without proteasomal inhibition (**Figure 2**), and decreases MG-132-triggered accumulation and degraded response (Schmukler et al., 2020). Namely, MG-132 blocks MFN-1 elimination in ApoE3 astrocytes but functions less in the ApoE4 setting. ApoE4 has probably compromised the degraded machinery before MG-132 treatment or eliminated the potency of inhibitor, which appears that ApoE4 effects may be equivalent to those of MG-132, the inhibition of MFN-1 degradation and ubiquitination in young mice. Moreover, CCCP-induced reduction of MFN-1 is lower in ApoE4 astrocytes than those of ApoE3 (Schmukler et al., 2020), indicating an impaired stress reaction as well. Therefore, ApoE4 may play significant roles in degraded machinery and mitochondrial fusion, or in certain steps before fusion so that MG-132 and CCCP fail to trigger corresponding stress signaling in the ApoE4 setting.

Like DRP1, the interfered effects of ApoE4 on MFN-mediated fusion are approximately established, but the regulatory mechanism in which APOE4 affects MFN metabolism is yet unclear, and several potential mediators are illustrated as follows. First, the levels of fusion proteins (MFN-1, MFN-2, OPA1) are growing and the polyubiquitinated level of MFN-2 is reduced, while the fission proteins (FIS1 and GLP1) are not distinctively altered in HEK293 cells overexpressing human Tau, and rat primary hippocampal neurons (Li et al., 2016), and the brain tissues from human Tau-transgenic mice (Kandimalla et al., 2016), indicating MFNs accumulation and mitochondrial dysfunction caused by human Tau. Second, excess Ca^{2+} in cytoplasm triggered by ApoE4 (Larramona-Arcas et al., 2020) partially blocks GTP-mediated oligomerization of MFN-1, thus resulting in impaired complex formation for fusion (Ishihara et al., 2017). Third, functional factors in the mitochondrial network link with each other by various chemical modifications. MFN-2 is phosphorylated by PINK1 for Parkin recruitment (Holness and Sugden, 2003; Bhupana et al., 2020; Du et al., 2021) and is ubiquitinated by Parkin (Zachari and Ktistakis, 2020), while PINK1 and Parkin are collectively regulated by ApoE4 (Simonovitch et al., 2019; Schmukler et al., 2020; Sohn et al., 2021).

Briefly, ApoE4 seems to interfere with mitochondrial fusion by blocking proteasomal degradation of MFN, and other potential regulations are required for further confirmation. Considering fission alteration, ApoE4-mediated fission failures probably couple with ApoE4-mediated fusion abnormalities and jointly deteriorate mitochondrial dynamics imbalance. It may be interesting to investigate whether there is a mutual implication between MFN-1 upregulation and DRP1 downregulation during ApoE4-impaired mitophagy. Overall, these results consistently suggest that the ApoE status specifically alters mitochondrial fission and fusion possibly *via* DRP1 and MFN-1 signaling, and the precise underlying mechanisms may be intriguing to be identified at different levels and by different measuring methods, such as activity, conformation, and chemical modification.

ApoE4 and Mitophagy Induction in AD

Mitophagy usually occurs in a ubiquitin-dependent manner, which is mediated by the classical PINK1/Parkin signaling pathway (Narendra et al., 2012), or in a receptor-mediated manner, which is independent of ubiquitin and regulated by NIX/BNIP3 (Sandoval et al., 2008; Li et al., 2021), FUNDC1 (Narendra et al., 2012; Chen et al., 2016), and BCL2-L-13 (Yamaguchi et al., 2016; Guan et al., 2018). Normally, PINK1 enters the mitochondria *via* translocase of outer mitochondrial membrane 40 (TOMM40) machinery, then is cleaved by PARL in a mitochondrial membrane potential (MMP)-dependent manner followed by degradation (Jin et al., 2010; Matsuda et al., 2010; Gottschalk et al., 2014). Upon mitochondrial depolarization, MMP collapse intervenes TOM complex thus leading to PINK1 accumulation on OMM and its autophosphorylation and dimerization (Jin et al., 2010; Narendra et al., 2012; Zachari and Ktistakis, 2020). PINK1 triggers the phosphorylation of ubiquitin, Parkin, and MFN-2, and couples with phosphorylated ubiquitin to facilitate Parkin recruitment. Activated Parkin further conjugates ubiquitin and boosts the ubiquitination of MIRO, voltage-dependent anion channel 1 (VDAC1) and MFNs on mitochondria (Zachari and Ktistakis, 2020), in which the ubiquitin chains can recruit p62, OPTN, NDP52, TAX1BP1, and NBR1 and facilitate mitophagy (Schmidt et al., 2021).

ApoE4 and PINK1/Parkin in AD

The PINK1-Parkin signaling pathway is one of the well-described molecular mechanisms inducing mitophagy (Narendra et al., 2012). Both PINK1 and Parkin have been widely investigated not only in PD but also in AD (El Gaamouch et al., 2016; Martín-Maestro et al., 2016). The levels of PINK1 and Parkin, as well as the related factors, are usually remarkably increased *in vivo* and *in vitro* models of AD and patients with AD (Mise et al., 2017; Ochi et al., 2020; Goudarzi et al., 2021), indicating various mitochondrial disturbances or dysfunctional mitophagy. However, the additional finding indicates upregulation of PINK1-Parkin-mediated mitophagy signaling improves cognitive behavior and memory in rats injected with $A\beta_{1-42}$ (Han et al., 2020). The elevation does not necessarily mean ongoing and activated mitophagy or a determined change in mitochondria status, as it may be caused by blocked degradation, available compensatory effect in response to various dysfunction in early AD progression, or exhausted compensatory storage along with aging in the terminal stage.

ApoE4 decreases MMP and ATP storage (Schmukler et al., 2020). Accordingly, lower cleaved PINK1 levels and higher full-length PINK1 (FL-PINK1) levels are found in ApoE4 astrocytes and hippocampal neurons from *APOE* ε4-TR mice (Simonovitch et al., 2019) (**Figure 2**), indicating the impaired proteolytic cleavage of PINK1 is in response to ApoE4-induced mitochondrial dysfunction (**Figure 2**). Incidentally, both the RNA level in *APOE* ε4 astrocytes and the total protein level of PINK1 in *APOE* ε4 carriers are decreased (Schmukler et al., 2020; Sohn et al., 2021), as well as PINK1-mediated phosphorylation of ubiquitin in *APOE* ε4 carriers is significantly suppressed (Sohn et al., 2021), suggesting inhibited expression of PINK1 and damaged potential reserve capacity of mitophagy. Taken together, it seems to reveal that under the ApoE4 condition, the proportion of FL-PINK1 is increased and the proportion of cleaved PINK1 is accordingly decreased at the basic of the reductive total amount of PINK1. These observations echo the alterations in AD abovementioned (Mise et al., 2017; Ochi et al., 2020; Goudarzi et al., 2021). Additionally, ApoE4 rather than ApoE3 astrocytes demonstrate lower level of PINK1 upregulation caused by MG-132 (Schmukler et al., 2020), similarly indicating an impaired degradation caused by ApoE4. However, an alternative study reported the level of the FL-PINK1 does not differ in the hippocampus of ApoE3 and ApoE4 mice (Simonovitch et al., 2019). Despite either FL-PINK1 is increased or unchangeable, the relation between PINK1 and ApoE4 is gradually established (Schmukler et al., 2020).

With enhancing *PARK2* mRNA synthesis (Schmukler et al., 2020), the total amount of Parkin and ubiquitinated Parkin levels are concomitantly dramatically increased in different hippocampal sections from *APOE* ε4-TR mice (Simonovitch et al., 2019) and ApoE4 astrocytes (Schmukler et al., 2020) (**Figure 2**). Following either the treatment with MG-132 or chloroquine, ApoE4 astrocytes display less increase of Parkin accumulation than those in ApoE3 astrocytes (Schmukler et al., 2020), indicating Parkin elevation is not only accounts for activating transcription, but its reduced proteasomal and mitophagic degradation, respectively (**Figure 2**). Similarly, accumulation of ubiquitinated Parkin caused by MG-132 only presents in ApoE3 astrocytes, indicating ubiquitinated Parkin also participates in proteasomal degradation and reconfirming the degradation blockage caused by ApoE4. This result is consistence with another finding regarding deficient degradation that ApoE4 directly interacts with lysosomal membranes, disrupts lysosomal acidification, and inactivates lysosomal hydrolase (Ji et al., 2002; Belinson et al., 2008; Zhu et al., 2015; Nuriel et al., 2017; Persson et al., 2017; Fote et al., 2022). It will be intriguing to examine the changes of mitophagic inducers and inhibitors on ApoE4-related pathology *in vivo*. Remarkably, autophagic inducer rapamycin has no effect on cleaved PINK1 level, but elevates FL-PINK1 level by enhancing PINK1 mRNA synthesis, decreasing MFN-1 and Parkin levels without transcriptional inhibition, and facilitates the PINK1/Parkin pathway in the ApoE4 astrocytes (Schmukler et al., 2020), leading to restoring mitochondrial metabolism, and correcting the altered medium pH without affecting cell number (Schmukler et al., 2020). These changes suggest that downstream Parkin accumulation follows upstream PINK1 deficiency, and rapamycin promotes mitophagy and remains its protective effects under ApoE4 condition, and it is likely to gain more attention as an AD therapeutical target.

Briefly, conservative speculation is that ApoE4 impedes mitophagy throughout protein synthesis and degradation, and there seems to exist a theoretical relationship between ApoE4, PINK1/Parkin-mediated mitophagy, and AD, which suggests an instructive hypothesis for neurodegenerative changes in AD involving various processes, including expression, cleavage, recruitment, ubiquitination, and degradation of PINK1 and Parkin at the molecular level. Nevertheless, the precise molecular mechanisms by which ApoE4 alters PINK1 and Parkin function

have not yet been elucidated, and it may involve a complicated regulated network of mitochondrial physiological events. Herein, we present the potential machinery focusing on several pivotal mitophagic factors as follows:

ApoE4 and the Regulators of PINK1/Parkin in AD

FOXO3a served as a transcription factor highly represented in the brain and a new target of AD diagnosis (Pradhan et al., 2020), that maintains cellular homeostasis against stresses for neuronal protection, and regulates the transcriptional activity of autophagy (*BECN1*, *ATG12*, *PIK3C3*) and mitophagic genes (*BNIP3* and *PINK1*) (Greer and Brunet, 2005; Murtaza et al., 2017; Cheng, 2019). Akt-involved phosphorylation of FOXO3a keeps exclusion from the nucleus and inhibits its transcriptional activity (Greer and Brunet, 2005). The lower protein level of FOXO3a and the higher phosphorylation level of FOXO3a-Ser253 are found in the postmortem human brain tissues from *APOE* ε4 carriers than non-carriers (Sohn et al., 2021), indicating that the transcriptional activity and expression of FOXO3a are considerably suppressed by *APOE* ε4 allele. Consistently, this is also supported by the results from immunoblot and correlation analysis that there is a concomitantly reductive transcription of its downstream genes (*BECN1*, *ATG12*, *BNIP3,* and *PINK1*) in *APOE* ε4 carriers. Collectively, ApoE4 mediated full-scale inhibition of mitophagy *via* FOXO3a signaling, including its expression, activity-dependent on chemical modification, and the induction of its downstream effects.

SIRT1 is a NAD-dependent deacetylase that is involved in the regulation of autophagy and mitophagy (Lee et al., 2008; Salminen and Kaarniranta, 2009; Jang et al., 2012; Ou et al., 2014) and displays neuroprotective implications in AD (Julien et al., 2009; Gomes et al., 2018). SIRT1 directly binds to the transcription factor FOXO3a and mediates FOXO3a deacetylation (Motta et al., 2004; Eijkelenboom and Burgering, 2013; Ou et al., 2014). The SIRT1-FOXO3a-BNIP3 axis is indispensable for the induction of PINK1-Parkin-dependent mitophagy (Yao et al., 2021). SITR1 activation elevates Parkin expression, thus facilitating Parkin-dependent mitophagic induction (Qiao et al., 2018). Given that ApoE4 interferences of SIRT1 function have been mentioned above, it may be attributable to the lower capacity reserve of mitophagy in AD progression. The neuroprotection of overexpressed SIRT1 indicates a promising target for AD.

BNIP3, A BH3-only member of the BCL2 family operating as a mitophagic receptor on OMM (Gao et al., 2020), stabilizes PINK1 protein onto mitochondria to boost PINK1-mediated mitophagy in hypoxic conditions (Zhang et al., 2016; Zachari and Ktistakis, 2020). Performed with mass spectrometry analysis and co-IP assay, FL-PINK1 is shown interact with BNIP3, and the BNIP3-PINK1 binding disrupts proteolytic cleavage of PINK1 to maintain the stabilization of FL-PINK1 for more Parking recruitment (Zhang et al., 2016). Moreover, BNIP3-mediated mitophagy is required for FOXO3a protections against temozolomide-induced DNA double-strand breaks (He et al., 2021), while FOXO3a interacts with the *BNIP3* upstream promoter and elevates BNIP3 expression (Lu et al., 2014). These results suggest that BNIP3 function as a hinge during mitophagy. Moreover, ApoE4 attenuates the expression of BNIP3 and PINK1 *via* Foxo3 signaling in *APOE* ε4 carriers (Sohn et al., 2021), thus impairing the responsiveness of mitophagy. This may enlighten an overlooked hinge for key mitophagic induction pathways, which closely involved PINK1-induced signaling and FOXO3a-induced signaling.

Sirtuin 3 (SIRT3) is a deacetylase, highly expressed in high-metabolic tissues, and strongly associated with mitochondrial quality (Meng et al., 2019). SIRT3 mediates FOXO3a activation and the PINK1-Parkin mitophagic induction to prevent cellular death (Jacobs et al., 2008; Li et al., 2018; Zhang et al., 2020). SIRT3 activation alleviates Aβ toxicity and repairs mitochondrial bioenergetics and maintains mitophagic activity and cognitive function in AD (Meng et al., 2019; Li et al., 2020; Yin et al., 2020; Yu et al., 2020; Zhang et al., 2020; Tyagi et al., 2021). SIRT3 expression was lower in the temporal cortices from *APOE* ε4 carriers than non-carriers (Yin et al., 2020). Additionally, SIRT3 expression is reduced and is rescued with ketones treatment only in *APOE* ε4-TR mice (Yin et al., 2019). Collectively, SIRT3, a downstream modulator of ApoE4, may provide a novel direction for AD pathology-related therapy targeting FOXO3a and PINK1-Parkin signaling.

TOMM40, a channel-forming subunit at OMM constituting the TOMM40 complex for protein import into mitochondria (Humphries et al., 2005; Manczak et al., 2011; Liu et al., 2018), is proposed as a novel biomarker of AD (Mise et al., 2017; Ochi et al., 2020). The TOMM-dependent signaling is well-known as a molecular hinge for PINK1/Parkin-mediated mitophagy (Bertolin et al., 2013). The defective TOMM complex is responsible for PINK1 accumulation and activation, as well as Parkin recruitment *via* direct interaction with TOMM40 (Bertolin et al., 2013). Compared to ApoE3 astrocytes, the protein level of TOMM40 is upregulated without growing transcriptional activity, indicating that augmented TOMM40 level in ApoE4 astrocytes may be on account for damaged degradation (Schmukler et al., 2020). This result is consistence with other findings regarding TOMM40 increase in the N_2a cells by proteomic profiling (Mise et al., 2017) and in both hippocampal homogenates and CA3 pyramidal cells from ApoE4 mice by immunoblot (Orr et al., 2019). Owing to the linkage disequilibrium with *APOE* (Simonovitch et al., 2019), *TOMM40* expression is closely associated with *APOE* expression (Mise et al., 2017), and *APOE-TOMM40-APOC1* variants are strongly associated with a high instance of AD (Gottschalk et al., 2014; Kulminski et al., 2022). With increasing age, *APOE* ε4 has closely linked to various *TOMM40* polymorphisms carried adverse impacts (Roses et al., 2013; Li et al., 2022), and alter the distribution and function of the TOMM40 haplotypes (Roses et al., 2010). which echoes the mentioned findings—more FL-PINK1 and Parkin, less cleaved PINK1 caused by ApoE4 (Simonovitch et al., 2019). Overall, TOMM40 polymorphisms and expression are associated with *APOE* ε4, and its degradation is blocked under an ApoE4-induced context, which may be helpful to explore the underlying mechanisms of AD.

VDAC1, a porin protein abundantly located at OMM that mediates ATP production and the trafficking of nucleotide

and metabolites, functions as a target for Parkin-directed poly-ubiquitin chains, and regulates Parkin recruitment (Sun et al., 2012), thus playing an indispensable role in PINK1/Parkin-mediated mitophagy (Geisler et al., 2010; Yamaguchi et al., 2016) and AD pathogenesis (Manczak and Reddy, 2012b; Shoshan-Barmatz et al., 2018; Chi et al., 2021). VDAC1 preliminarily showed an increase in ApoE4-N_2a cells performed by proteomic profiling assays (Orr et al., 2019), which is appealed to further experimental verification. Interestingly, a recent study reports the binding of ApoE and VDAC induces the continual opening of the mitochondrial permeability transition pore thus resulting in MMP collapse and electronegative LDL-mediated mitochondrial disorders and impaired degradation (Chen et al., 2020), which may partially account for the VDAC1 elevation abovementioned (Orr et al., 2019). Specifically, it is shown both ApoE3 and ApoE4 are colocalized with VDAC *via* double-labeling analysis, and reconfirmed the interaction without isoform-dependent difference *via* co-IP in H9c2 cells, a type of embryonic rat heart-derived cells (Chen et al., 2020). Although discrepant interaction between ApoE3 and ApoE4 could not be found, the finding enlighten the researchers to broadly examine the ApoE-VDAC interaction in neuronal models, including cell lines of neurons or glia, primary neuronal cells, and brain tissues from *APOE*-TR mice or AD model mice, even the *APOE* ε4 carriers and AD subjects, in order to explore whether the interaction exists in the neuronal system, whether there is a differential interaction between ApoE3 and ApoE4, and whether it is associated with AD pathogenesis. Incidentally, the VDAC1-Aβ and VDAC1-Tau interaction is confirmed by double-labeling analysis and co-IP in the brains of AD subjects and several AD model mice (Manczak and Reddy, 2012b), while it is well known that ApoE4 mediates Aβ aggregation and Tau hyperphosphorylation (Ellis et al., 1996; Brecht et al., 2004). Looking at the above factors, it is supposed that the ApoE-VDAC binding cooperates with the VDAC1-Aβ and VDAC1-Tau interaction conjointly blocks mitochondrial pores as synergistic effects, ultimately contributing to mitochondrial dysfunction, defective mitophagy, and aberrant accumulation of damaged mitochondria, interrupting energy supply and aggravating synaptic dysfunction in AD.

Aβ aggregation causes reductive cytosolic Parkin and PINK1 levels in the cytoplasm (Kerr et al., 2017); Aβ also binding to Parkin and autophagic vacuoles in the distal axons of APP-mutant mouse cells (Cai and Tammineni, 2016; Reddy and Oliver, 2019). Presenilins mutations interrupt PINK1 elevation and PINK/Parkin-dependent mitophagic cycle (Goudarzi et al., 2021). More Parkin recruitment of cytosolic to depolarized mitochondria is shown in human APP-transgenic neurons (Cai and Tammineni, 2016). Dysfunctional Parkin translocation and recruitment result from Tau accumulation and detrimental interactions with Tau (Goudarzi et al., 2021).

Collectively, ApoE4 and PINK1-Parkin comprise a potential mitochondrial signaling cascade response pathway, and these observations indicate ApoE4-mediated inhibition on PINK1-Parkin mitophagy *via* multi-faced downstream regulators (Sohn et al., 2021). The data provide new insights into the role of ApoE4 in mitophagic deficiency to develop a potential therapeutic target for AD.

CONCLUSION AND PROSPECTS

Deficient mitochondrial quality control is established to interfere with cellular bioenergetic metabolisms and neuronal survival, leading to the occurrence and development of neurodegenerative disorders (Chinnery, 2015). Based on the multi-faceted roles that mitophagy plays in AD pathogenesis (Salminen et al., 2013), we integrate various overwhelming evidence ranging from cellular models to clinical patients that autophagic and mitophagic dysfunction result from ApoE4—multiple interferences of general autophagic processes, fission inhibition, fusion-related protein accumulation, PINK1/Parkin signaling blockage—and highlight additional findings that helps to further elucidate the cross talk of ApoE4 and its effector, as well as the regulations of mitochondrial dynamics events.

Despite current studies about mitophagic control, some important issues are required to be addressed. First, ApoE4 participates in diverse mitophagic signaling pathways at various processes in direct or indirect manners (Horner et al., 2020; Schmukler et al., 2020; Yin et al., 2020; Liang et al., 2021b; Qi et al., 2021; Eran and Ronit, 2022). Taking the cross talk among these signaling pathways into account, it is proposed to further study the interconnected interactions between different pathways, and distinguish which of them plays a predominant role in the pathological consequences of ApoE4. Moreover, certain factors play multiple roles in mitochondria metabolism. SIRT1 (Lee et al., 2008; Jang et al., 2012; Lu et al., 2014; Ou et al., 2014; Qiao et al., 2018; Yao et al., 2021), Ca^{2+} (Cereghetti et al., 2008; Ishihara et al., 2017; Barazzuol et al., 2020), Aβ (Manczak et al., 2011; Cai and Tammineni, 2016; Kerr et al., 2017; Reddy and Oliver, 2019), and Tau (Manczak and Reddy, 2012a; Abtahi et al., 2020; Goudarzi et al., 2021; Kandimalla et al., 2021) function throughout autophagic general processes and mitochondria-specific processes and affect the balance between mitophagy, mitochondrial biogenesis, and mitochondrial dynamics. Second, concerning high AD prevalence in females, it is recommended to highlight the probable role of gender differences or interference in various behavior assessments or molecular indicators in clinical or non-clinical studies in order to find more meticulous findings underlying the complicated effects of *APOE* genotype. Third, the neuro-degeneration processes may share a common mechanism with AD and other neurodegenerative diseases. ApoE has been extensively studied in multiple fields and displays new findings, such as the interaction of ApoE4-*TFEB* promoter (Parcon et al., 2018), ApoE4-*SIRT1* promoter (Theendakara et al., 2016; Lima et al., 2020), and particularly ApoE-VADC (Chen et al., 2020) in myocardial cells, which deserves extending to neuronal researches, particularly mitophagy in AD. There is a preference for detailed, multivariate, and diversified indicators to investigate molecular and functional alterations in new aspects. From a molecular perspective, it may be worthy to differentiate the features of the specific interactions more detailedly, including specificity, affinity, stability, intermolecular force, and other quality at the submolecular level. Fourth, because only few studies have reported OPA1, FIS1 function,

and receptor-mediated mitophagy differed from an *APOE*-genotype perspective, hence, completing a related investigation may be helpful to better understand the complicated alterations in AD (Sun et al., 2014; He et al., 2019). Fifth, mitophagic stimulation may be beneficial to tissue homeostasis, as judged by the neuroprotective implication of rapamycin has been comprehensively assessed (Schmukler et al., 2020). Studies may be intriguing to investigate the clinical benefits of more known autophagic or mitophagic inducers or other drugs, such as GRP75 inhibitor (Liang et al., 2021b), *in vivo* and *in vitro* studies and further develop specific therapies.

In general, mitophagy is a multifunctional event preventing AD pathogenesis along with multiple challenges to its beneficial effects. Current findings of the ApoE4 role of mitophagy in AD seem to be limited to some extent, and remain controversial still need further investigation in detail. Discovering the gaps in the underlying mechanisms are greatly enlightened to screen for possible and predominant mechanisms and open a new avenue of research to facilitate earlier diagnosis or potential neuroprotective therapies for AD.

AUTHOR CONTRIBUTIONS

GC had the idea for the article and made the final approval of version to be submitted. HC wrote and critically revised the manuscript the work. YiJ and FC supervised the overall writing and edited the manuscript. GH and LZ performed the literature search, sorting, and integration. FS and MZ provided guidance, helpful discussion, and careful revision. YC and YaJ helped the schematic diagrams. All authors contributed to the article and approved the submitted version.

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The Effect of Lifetime Noise Exposure and Aging on Speech-Perception-in-Noise Ability and Self-Reported Hearing Symptoms: An Online Study

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Animal research shows that aging and excessive noise exposure damage cochlear outer hair cells, inner hair cells, and the synapses connecting inner hair cells with the auditory nerve. This may translate into auditory symptoms such as difficulty understanding speech in noise, tinnitus, and hyperacusis. The current study, using a novel online approach, assessed and quantified the effects of lifetime noise exposure and aging on (i) speech-perception-in-noise (SPiN) thresholds, (ii) self-reported hearing ability, and (iii) the presence of tinnitus. Secondary aims involved documenting the effects of lifetime noise exposure and aging on tinnitus handicap and the severity of hyperacusis. Two hundred and ninety-four adults with no past diagnosis of hearing or memory impairments were recruited online. Participants were assigned into two groups: 217 "young" (age range: 18–35 years, females: 151) and 77 "older" (age range: 50–70 years, females: 50). Participants completed a set of online instruments including an otologic health and demographic questionnaire, a dementia screening tool, forward and backward digit span tests, a noise exposure questionnaire, the Khalfa hyperacusis questionnaire, the short-form of the Speech, Spatial, and Qualities of Hearing scale, the Tinnitus Handicap Inventory, a digits-in-noise test, and a Coordinate Response Measure speech-perception test. Analyses controlled for sex and cognitive function as reflected by the digit span. A detailed protocol was pre-registered, to guard against "p-hacking" of this extensive dataset. Lifetime noise exposure did not predict SPiN thresholds, self-reported hearing ability, or the presence of tinnitus in either age group. Exploratory analyses showed that worse hyperacusis scores, and a greater prevalence of tinnitus, were associated significantly with high lifetime noise exposure in the young, but not in the older group. Age was a significant predictor of SPiN thresholds and the presence of tinnitus, but not of self-reported hearing ability, tinnitus handicap, or severity of hyperacusis. Consistent with several lab studies, our online-derived data suggest that

older adults with no diagnosis of hearing impairment have a poorer SPiN ability and a higher risk of tinnitus than their younger counterparts. Moreover, lifetime noise exposure may increase the risk of tinnitus and the severity of hyperacusis in young adults with no diagnosis of hearing impairment.

Keywords: noise exposure, aging, cochlear synaptopathy (CS), age-related hearing loss (ARHL), speech perception in noise (SPiN), self-reported hearing, tinnitus, hyperacusis

INTRODUCTION

Presbycusis, which is also known as age-related hearing loss (ARHL), is a common condition in older adults caused by a combination of factors including lifetime cumulative noise exposure, genetic susceptibility, metabolic changes in the cochlea, and intake of ototoxic substances (Gordon-Salant et al., 2010). Excessive noise exposure and aging, as two independent factors, are associated with damage to the outer hair cells, the inner hair cells, and the spiral ganglion cells (Wang et al., 2002; Gates and Mills, 2005; Sergeyenko et al., 2013; Jayakody et al., 2018). This damage often results in deterioration of hearing sensitivity, loss of frequency selectivity, and poorer temporal resolution (Ashmore et al., 2010).

The cochlear synapses which connect inner hair cells with afferent auditory nerve fibers (ANFs) have been shown to degenerate in several animal species because of acoustic over-exposure and aging, well before outer and inner hair cells are lost. Thus, this cochlear synaptopathy (CS) can take place in the absence of hearing threshold elevation in the standard audiometric range (Kujawa and Liberman, 2009; Lin et al., 2011; Makary et al., 2011; Furman et al., 2013; Sergeyenko et al., 2013; Viana et al., 2015; Valero et al., 2017; Hickman et al., 2018; Parthasarathy and Kujawa, 2018; Wu et al., 2019; Fernandez et al., 2020). However, CS may be accompanied by permanent threshold elevations at the highest frequencies of the hearing range, which reflect the extreme basal cochlear regions (Hickox et al., 2017). Post-mortem human temporal bone data confirm an age-related synapse and ANF loss in older adults with no otologic symptoms (Viana et al., 2015; Wu et al., 2019, 2021). Noise exposure and aging seem to preferentially affect low-to-medium-spontaneous-rate high-threshold ANFs in some rodents (Schmiedt et al., 1996; Furman et al., 2013) though not in other species (Suthakar and Liberman, 2021).

It is suggested that the loss of low-to-medium spontaneous rate ANFs due to CS results in poorer temporal resolution for moderate-to-high-level acoustic stimuli such as speech (Kujawa and Liberman, 2009; Sergeyenko et al., 2013; Bharadwaj et al., 2014; Shaheen et al., 2015; Fernandez et al., 2020). Several human studies have investigated the effects of noise exposure and aging on speech-perception-in-noise (SPiN) thresholds. The majority of studies that investigated young normal-hearing humans with extensive noise exposure have failed to establish an association between lifetime noise exposure and SPiN performance (for reviews see Bramhall et al., 2019 and Le Prell, 2019). In contrast, several studies have documented higher (i.e., worse) SPiN thresholds among older adults with normal/near-normal audiograms compared to their younger counterparts (Pichora-Fuller et al., 1995; Kim et al., 2006; Füllgrabe et al., 2015; Vermeire et al., 2016; Babkoff and Fostick, 2017; Patro et al., 2021). However, it is worth highlighting that those studies did not attempt to isolate the effects of CS on SPiN performance from other factors which can potentially affect SPiN at an older age, such as central auditory neural degeneration (which may decrease temporal resolution; Caspary et al., 2008; Ouda et al., 2015), poorer cognitive function (Humes and Dubno, 2009; Kamerer et al., 2019), and worse extended high-frequency thresholds (Stelrnachowicz et al., 1989; Snell et al., 2002). The current study attempted to isolate the effects of auditory factors such as CS on SPiN ability by employing a cognitive task to control for the effects of age-related central and cognitive decline with regards to SPiN performance.

Johannesen et al. (2019) investigated the effects of noise exposure and aging in audiometrically normal adults (n = 94) aged 18–68 years using sentences from the hearing in noise test fixed at 65 dB SPL and disyllabic words at 50-, 65-, and 75-dB SPL. The masking noise was changed adaptively and was either speech-shaped noise or the international female fluctuating masker. Hearing-in-noise-test thresholds using both the speech-shaped-noise and the international female fluctuating maskers were significantly worse for older adults. No effects of age were evident on disyllabic words when combined across different speech levels, using either masker. The authors reported no interaction between age and the speech presentation levels in relation to SRTs obtained using disyllabic words.

Prendergast et al. (2019) and Carcagno and Plack (2021) studied the effects of various lifetime noise exposures (i.e., occupational, recreational) and age in audiometrically normal/near normal adults (n = 156 and n = 102, respectively) using the Coordinate Response Measure (CRM) speech task and the Digits In Noise (DIN) test. Carcagno and Plack (2021) employed low-pass-filtered speech stimuli (with a cut-off frequency of 3 kHz) in both SPiN tasks. CRM Stimuli were presented at low (i.e., 39 dB SPL) and high (i.e., 74 dB SPL) levels embedded in pink band-pass filtered noise (3–8 kHz) to reduce the contribution of basal cochlear generators. Prendergast et al. (2019) presented both the CRM (embedded in competing speech utterances) and DIN (embedded in speech-shaped noise of bandwidth of 0–10 kHz) stimuli at 40- and 80-dB SPL. Neither study found a significant effect of either lifetime noise exposure or age on the CRM thresholds (at either level).

Abbreviations: ARHL, Age-related hearing loss; ANFs, Auditory nerve fibers; CS, Cochlear synaptopathy; SPiN, Speech perception in noise; DIN, Digits in noise; CRM, Coordinate Response Measure; THI, Tinnitus Handicap Inventory; SSQ12, The abbreviated form of the Speech Spatial and Qualities of Hearing Questionnaire.

However, Prendergast et al. (2019) reported that older age was unexpectedly associated with better DIN thresholds at low stimulus levels while higher lifetime noise exposure was associated with better thresholds at high stimulus levels. In contrast, Carcagno and Plack (2021) found that neither age nor noise exposure had effects on DIN thresholds using band-limited stimuli. In their secondary analyses, Prendergast et al. (2019) found that the 16 kHz absolute threshold was a significant predictor of DIN scores.

Banh et al. (2012) and Carcagno and Plack (2021) studied the effect of aging on self-reported hearing ability using the SSQ12 and SSQ questionnaires, respectively (n = 96 and n = 102, respectively). Both studies found that older age is not associated with worse SSQ12 scores in audiometrically normal older adults (as defined by normal hearing thresholds up to 4 kHz). However, Banh et al. (2012) found that older adults with moderate sensorineural hearing loss exhibited significantly worse SSQ12 scores compared to their younger and older audiometrically-normal counterparts.

Both noise exposure and aging are well-established risk factors for tinnitus and hyperacusis (Gates and Mills, 2005; Kim et al., 2015; Paulin et al., 2016; Oosterloo et al., 2021). According to the British Tinnitus Association, tinnitus is defined as "*The perception of sound in the absence of any corresponding external sound. This noise may be heard in one ear, in both ears, in the middle of the head, or it may be difficult to pinpoint its exact location. The noise may be low, medium, or high-pitched. There may be a single noise or two or more components. The noise may be continuous, or it may come and go*" (Mancktelow, 2022). Hyperacusis is defined as pathological intolerance and hypersensitivity to moderate sounds (Tyler et al., 2014).

The effects of both tinnitus and hyperacusis are commonly quantified both clinically and for research purposes using self-reported psychometrically validated questionnaires such as the tinnitus handicap inventory (THI; Newman et al., 1996) and the Khalfa hyperacusis questionnaire (Khalfa et al., 2002). The THI is composed of 25 questions that evaluate the severity and impact of tinnitus on the participant's daily life functioning (Newman et al., 1996). The total maximum score of the THI is 100 points, with a higher score reflecting a more severe tinnitus handicap (Newman et al., 1996). The Khalfa hyperacusis questionnaire consists of 14 questions that investigate intolerance to sounds through common daily life settings (Khalfa et al., 2002). Each question is scored on a 4-point scale with 1 point reflecting almost no hypersensitivity to moderate sounds and 4 points corresponding to the maximum intolerance to moderate sounds (Khalfa et al., 2002).

Some studies have quantified the effect of lifetime noise exposure on the presence of tinnitus and its handicap and on hyperacusis. For instance, Guest et al. (2017) compared the lifetime noise exposure of two groups of young audiometrically-normal hearing groups: a tinnitus group (n = 20) and a control group (n = 20). The authors found that the tinnitus group exhibited significantly higher lifetime noise exposure compared to the control group. Couth et al. (2020) employed the THI and the Khalfa hyperacusis questionnaire to compare tinnitus handicap and hyperacusis severity, respectively, in two groups of young audiometrically-normal adults: musicians (n = 85) and non-musicians (n = 52). Although the mean THI scores in both groups corresponded to the no handicap/slight handicap category, the mean THI score of musicians was significantly higher than that of non-musicians. Similarly, the authors found that musicians exhibited significantly higher (i.e., worse) hyperacusis scores compared to their non-musician counterparts. Yilmaz et al. (2017) quantified the severity of hyperacusis using the Turkish version of the Khalfa hyperacusis questionnaire among 536 university students. Although this study did not quantify noise exposure, nor did it quantify the hearing status of participants, students who reported being regularly exposed to loud noises had significantly higher hyperacusis scores compared to those without self-report of excessive noise exposure.

The current study, which employed novel online instruments to collect both behavioral and self-report hearing data remotely, aimed to assess and quantify the effects of lifetime noise exposure and aging on the hearing ability of older adults in the United Kingdom (UK). It is worth highlighting that this online study, unlike the majority of previous studies in the literature, was not limited to a sample of participants who were able and willing to attend a laboratory but rather targeted a broader UK demographic that may be exposed to a variety of noise sources and may be composed of various ethnic and socio-cultural backgrounds. The study compared the effects of both noise and aging on (i) SPIN thresholds using an online DIN test, (ii) self-reported hearing ability, and (iii) the presence of tinnitus. In exploratory data analyses, we determined the effects of lifetime noise exposure and aging on (i) the SPiN thresholds using an online version of the CRM test, (ii) tinnitus presence and handicap, and (iii) the severity of hyperacusis. We hypothesized that higher lifetime noise exposure and older age would be associated with (i) higher SPiN thresholds, (ii) worse self-reported hearing ability, (iii) a higher proportion of participants with tinnitus, (iv) worse tinnitus handicap, and (v) greater severity of hyperacusis. We found no evidence for poorer SPiN performance, worse self-reported hearing, or higher severity of tinnitus handicap as a function of higher lifetime noise exposure in either age group. Higher prevalence of tinnitus and greater severity of hyperacusis were associated with higher lifetime noise exposure in the young, but not in the older, group. Finally, aging was associated with poorer SPiN performance and a higher prevalence of tinnitus.

MATERIALS AND METHODS

This study was pre-registered on the Open Science Framework before the beginning of the data collection as part of a larger lab-based research project. Due to the COVID-19 pandemic, the original lab-based study plan was changed, and an amendment was put in place to reflect the intention to collect data online before the actual data collection started. All the hypotheses, data collection procedures, and primary statistical analyses of the current online study are in line with the pre-registered protocol as shown in the amended document.[1]

[1] https://osf.io/jzu4t/

Participants

A total of 295 adult participants for whom English was either their native (n = 227) or second language (n = 68) were recruited into two age groups ("young" n = 217, 151 females, age range: 18–35 years, mean age: 24.6 years; and "older" n = 78, 50 females, age range: 50–70 years, mean age: 58.0 years) through online advertising including social media, the University of Manchester research volunteering platform, and various young and older adult charities and societies in the United Kingdom.

Participants reported no diagnosis of hearing loss, current middle-ear pathologies, past ear surgeries, head trauma, ototoxic exposure, neurological disorders, or past diagnosis of cognitive impairments. Forty-eight participants were excluded due to reporting a past diagnosis of hearing impairments (n = 15), a suspicion of (based on the AD8 dementia screening tool) or past diagnosis of cognitive/memory impairment (n = 14), or being in an age group that did not match the inclusion criteria of the current study (n = 19).

In order to test the effect of age, independent of noise exposure, on the different primary and secondary outcome measures, participants in both age groups with low lifetime noise exposure (as defined below in section "Statistical Analyses") were allocated into low-noise groups. A total of 175 participants (mean age = 24.6, females = 122) and 56 participants (mean age = 58.0, females = 34) formed the young and older low noise groups, respectively.

Upon participation, participants provided their written informed consent online for taking part in the study. A prize draw was offered as an incentive to participants. The study procedures were approved by the University of Manchester Research Ethics Committee (ethics application reference: 2020-8884-13533).

Online Instruments

This study was carried out entirely using the Research Electronic Data Capture (REDCap) platform hosted at the University of Manchester (Harris et al., 2009, 2019). REDCap allows online research data collection through a secured electronic platform that allows data validation, integration, manipulation, and export to different statistical packages. All 295 participants completed all the online instruments, except for the DIN test, CRM task, and THI questionnaire. All native English participants were invited to perform the SPiN tasks. However, a subset of them (141 participants; 62% of native English participants; 48% of the total sample) completed the DIN and CRM tasks. Since 67 participants out of 295 (23% of the total sample) reported tinnitus, the THI questionnaire was performed by 67 participants only.

Otologic Health and Demographic Information

The clinical and demographic online questionnaire (see **Supplementary Material**) was used to collect relevant demographic as well as hearing and general health information. Demographic questions covered participants' age, sex, educational attainment, and contact details. Participants were asked about their otologic and hearing health histories such as past ear/hearing disorders or surgeries, family history of hearing impairment, tinnitus, hyperacusis, balance problems, and intake of ototoxic drugs. Moreover, participants were asked to identify any past or current chronic health conditions and/or disabilities and subsequent intake of medications.

Dementia Screening

Since this study measured both self-reported hearing ability and SPiN in older adults as outcome measures, it was essential to minimize differences in performance due to central cognitive factors. The Alzheimer's Disease (AD8) dementia screening tool (see **Supplementary Material**) was hence used in the form of an online self-reported questionnaire to screen for mild cognitive decline secondary to dementia. This dementia screening test is considered a time-efficient, valid, and reliable tool with high sensitivity and specificity (Galvin et al., 2005; James et al., 2006). The AD8 dementia screening online questionnaire is composed of eight statements describing different executive cognitive functions related to everyday activities (e.g., the ability to recall the correct month/year). Participants judged whether they think there has been a negative change to each of the relevant abilities. Participants with suspected dementia, based on AD8 answers, were excluded from the study and were encouraged to seek specialist advice.

Noise Exposure

Lifetime noise exposure was estimated using an online questionnaire based on the Noise Exposure Structured Interview (Guest et al., 2018a). This approach is based on the work of Lutman et al. (2008) and has been frequently used in recent years in some CS research studies (Guest et al., 2017, 2018b; Prendergast et al., 2017a,b, 2018, 2019; Causon et al., 2020; Couth et al., 2020; Shehorn et al., 2020). The noise exposure questionnaire (see **Supplementary Material**) is composed of four sections: occupational noise, recreational noise, firearm noise, and earphone/headphone noise exposure. In each section, activities that constitute potentially unsafe noise exposure (i.e., noise levels > 80 dBA) were selected/identified. For each noise exposure activity, participants then estimated the vocal effort required to converse in the selected situation, or the volume control level in the case of noise exposure from personal listening devices. These values were used to estimate the sound pressure level in dBA (Lutman et al., 2008; Guest et al., 2018a). Then participants specified the number of years, weeks per year, days per week, and hours per day of exposure for each selected activity. Finally, participants stated whether hearing protection was used for each of the specified activities and selected their type (if used). For each activity, the magnitude of lifetime noise exposure was determined by applying the following formula:

$$U = 10^{(L-A-90)/10} \times \frac{T}{2080}$$

Where U = units of noise exposure (energy); L = level (dBA); A = attenuation of ear protection; T = total exposure time. The results were summed across activities to give total units of noise exposure for each participant. Participants with 0 units of lifetime noise exposure were assigned a value of 0.00001. One raw unit of noise emission (U) equates to continuous workplace exposure of 90 dB(A) for one entire working year (2,080 h). For primary

and secondary data analysis purposes, the units of lifetime noise exposure were log-transformed [$\log_{10}$(U)] to produce a normally distributed variable. Hence, one logarithmic unit is equivalent to a factor of 10 in terms of lifetime noise exposure energy.

Cognitive Function

The digit span test with its forward and backward versions (Wechler, 1997) was incorporated as an online tool on REDCap as a measure of attention and short-term memory span. Numbers in both versions of the digit span test were presented visually on screen in an animated sequence, starting at two digits for a trial run, with each digit appearing for 1 s, and with a delay of 1 s between digits. The actual test began at two digits with the same temporal characteristics as for the trial run. For the forward digit span test, participants entered the same sequence of digits they saw (e.g., sequence: 3 2 7, correct answer: 3 2 7). For the backward digit span test, participants inputted the reverse sequence of digits (e.g., sequence: 3 2 7, correct answer: 7 2 3).

Each correct answer (all digits reported in the correct order) led to a new number sequence with an additional digit, up to a maximum of nine digits. If the entered answer was incorrect, an alternative sequence of numbers was given with the same number of digits. If the answer was incorrect twice for the same number of digits, the test ceased. The highest number of digits correctly identified was counted as the participant's score on both the forward and backward digit span tests.

Hyperacusis

The degree of sensitivity and intolerance to sounds was evaluated using the Khalfa hyperacusis questionnaire (see **Supplementary Material**), which consists of 14 items (Khalfa et al., 2002). The items cover attentional, social, and emotional aspects related to sound intolerance. Participants judged each statement using a four-point scale such that a "no" answer corresponds to 0 points, "yes, a little" corresponds to 1 point, "yes, quite a lot" corresponds to 2 points, and "yes, a lot" corresponds to 3 points. The scores of all statements were added (per subject) and a mean score (out of 4 points) was calculated per participant.

Self-Reported Hearing Ability

In order to evaluate participants' subjective hearing ability in real-world situations, the short form of the Speech, Spatial, and Qualities of Hearing scale (SSQ12) was used (Noble et al., 2013; see **Supplementary Material**). The SSQ12 questionnaire is composed of five statements from the speech domain, three statements from the spatial domain, and four statements from the qualities of the hearing domain. The SSQ12 was chosen instead of the full version SSQ in this study since it is faster to complete and may have adequate validity, reliability, and sensitivity compared to the full version of the SSQ (Noble et al., 2013; Ou and Kim, 2017).

Participants were asked to rate each statement of the SSQ12 using a 0–10 scale such that a higher score represents better performance. If a statement does not apply to a participant, they can select the "not applicable" option. A mean SSQ12 score was calculated per participant based on all applicable statements that they rated (non-applicable statements were unscored).

Tinnitus Handicap

The THI was used to assess the severity and impact of tinnitus on the participant's daily life functioning. The THI (see **Supplementary Material**) is a standardized self-reported questionnaire that is composed of 25 questions that cover the potential physical, psychological, social, emotional, and occupational impact of tinnitus (Newman et al., 1996). Participants were asked whether they currently suffer from tinnitus, defined by the British Tinnitus Association (Mancktelow, 2022) as "*The perception of sound in the absence of any corresponding external sound. This noise may be heard in one ear, in both ears, in the middle of the head, or it may be difficult to pinpoint its exact location. The noise may be low, medium, or high-pitched. There may be a single noise or two or more components. The noise may be continuous, or it may come and go*."

Participants who reported suffering from tinnitus were asked to answer each question of the THI by judging the occurrence of each situation by either choosing one of the following choices "*Always*," "*Sometimes*," or "*Never*." Statements answered with "*Always*" were allocated 4 points, whereas those answered with "*Sometimes*" received 2 points. Statements answered with "*Never*" were given 0 points. The THI score was then determined per participant by summing the corresponding scores across questions.

Speech-in-Noise Tasks

Participants completed the DIN and CRM tests *via* a custom-designed web page, mouse/trackball or trackpad, and their own headphones or earphones. The DIN was used as the primary outcome measure to determine SPiN ability, while the CRM result was used for exploratory analyses. Both the SPiN tasks are comprised of closed-set, simple, familiar words, limiting the effects of some linguistic factors which could compromise sensitivity to synaptopathy-related SPiN deficits (Guest et al., 2018b).

Since participants performed both tasks individually, it was important to ensure that presentation levels were comfortably within the dynamic range of hearing, so that (a) performance was not limited by the audibility of the target speech and (b) stimuli were not uncomfortably loud. Participants completed an initial subjective calibration phase, involving speech stimuli presented at two sound levels, separated by 25 dB. They were instructed to adjust the volume control on their computers so that the low-level speech was clear, and the high-level speech was loud but not uncomfortable. Subsequent test stimuli were presented at an RMS level 20 dB above that of the low-level calibration stimulus and 5 dB below that of the high-level calibration stimulus. Since threshold signal-to-noise ratios were unlikely to ever fall below −20 dB, this was designed to ensure that, during testing, target speech did not become inaudible, even at low signal-to-noise ratios.

Participants were instructed to run both tests in a quiet room, away from distractions, using their personal computers or laptops (i.e., not smartphones or tablets), and to listen to the tasks through their headphones/earphones (i.e., not built-in speakers). Each listening task involved one training block which lasted

about 4 min and one 5-min testing block. In order to maintain the participant's attention and engagement, visual feedback was presented following each trial, showing whether the subject's response was correct or incorrect and the difficulty level they reached at each trial.

Online Digits-in-Noise Test

Thresholds for the DIN task are thought to be primarily determined by the health of the peripheral auditory system rather than by central factors (Heinrich et al., 2015). Therefore, this task may help to capture peripheral auditory factors associated with SPiN ability by minimizing variability due to cognitive factors. Moreover, Heinrich et al. (2015) showed that performance on the DIN task may be associated with self-reported auditory function using the SSQ tool, which suggests that it may reflect a realistic representation of real-life listening abilities. Hence, the DIN was used as the primary measure of SPiN ability in this study.

DIN target phrases involve a carrier phrase and three digits ranging from 1 to 9 ("*The digits {digit 1} {digit 2} {digit 3}*"), embedded in speech-shaped background noise (Smits et al., 2004). The digits and background noise were low-pass filtered at a knee-point of 8 kHz to limit the effects on the performance of differences in the high-frequency responses of participants' headphones/earphones. Stimuli were presented diotically and were spoken in English by a British female speaker. Participants were instructed to enter the three digits on a numeric keypad on the web interface. A response was counted as correct if participants entered 2/3 or 3/3 digits correctly. The signal-to-noise ratio was varied using a two-down, one-up adaptive rule, with four initial turn points (6 dB step size) and six subsequent turn points (2 dB step size). The signal-to-noise ratios at the final six turn points was averaged to yield the threshold. Before each of the actual scored DIN and CRM tasks began, participants performed short (4-min) practice blocks for both tests.

Online Coordinate Response Measure Speech Test

The CRM test involves phrases of the form "*Ready {call-sign}, go to {color} {number} now*" (Bolia et al., 2000), articulated by four male and four female British-English talkers (Kitterick et al., 2010). The stimulus library consisted of eight call signs, four colors (green, red, blue, and white), and four numbers (1, 2, 3, and 4). The target speech was a randomly selected phrase with the call-sign "*Baron*." The competing speech was composed of two simultaneously presented phrases, spoken by the same or a different talker, each randomly selected from the library excluding the call-sign "*Baron*." As with the DIN test, the CRM speech stimuli and the masker were low-pass filtered at a knee-point of 8 kHz. The phrases were spatialized by convolving them with head-related impulse responses so that the target was presented at 0° and the two maskers at −60° and + 60°. Participants were instructed to identify the color and number associated with the call-sign "*Baron*" only, entering them *via* mouse and browser in a 16-alternative, forced-choice paradigm.

During the CRM test, the signal-to-noise ratio was varied using an adaptive two-down, one-up stepping rule with a 6-dB step size for the first four turnpoints and a 2-dB step size for the final six turnpoints. The threshold was estimated by taking an average of the signal-to-noise ratio at the final six turnpoints.

Statistical Analyses

Data were analyzed using the statistical package for social sciences (SPSS) version 26 software, while figures were generated using R (R Core Team, 2020). The main analyses determined the effects of lifetime noise exposure (in the older group) and age (in the low-noise groups) on (i) self-reported hearing ability, (ii) the presence of tinnitus, and (iii) SPiN performance as reflected by DIN thresholds. Multiple linear regression models were used to test (i) and (iii), while logistic regression models were employed to test (ii).

For all primary and exploratory research questions, the predictor variables were lifetime noise exposure and age, while the sex of participants and their cognitive function (as reflected by the forward and backward digit span test scores) were considered covariates in all the statistical models. The effect of lifetime noise exposure on the different outcome measures in the older group was a primary focus of this study because the majority of previous studies involved young audiometrically normal adults, with only a few studies assessing the perceptual effects of noise-induced CS in older normal-hearing adults (Valderrama et al., 2018; Prendergast et al., 2019; Yeend et al., 2019; Carcagno and Plack, 2021).

In order to assess the effect of age in the primary and exploratory research questions independent of lifetime noise exposure, only participants with low lifetime noise exposure were included in these analyses. This is defined as less than 1.0 unit of lifetime noise exposure in the protocol pre-registered prior to the beginning of data collection. This criterion is consistent with the classification of Prendergast et al. (2017b) of "low" lifetime noise exposure, corresponding to the 25% lowest lifetime noise exposure scores of their cohort ($n = 141$).

Alpha level was adjusted for six multiple comparisons using the Bonferroni-Holm method, with a familywise error rate of < 0.05. Exploratory analyses were performed to test the effect of lifetime noise exposure (in the young group) and age (in the low-noise group) on (i) the severity of hyperacusis, (ii) tinnitus handicap, and (iii) SPiN performance as shown by the CRM thresholds. Multiple linear regression models were employed to test the effects of lifetime noise exposure and age on the secondary outcome variables. The covariates of sex and cognitive ability were accounted for in the multiple linear regression models of the secondary analyses.

Further exploratory multiple regression models were performed to assess the interaction between lifetime noise exposure and age on (1) DIN thresholds, (2) CRM thresholds, (3) SSQ12 scores, (4), and the proportion of participants with tinnitus, (5) the THI scores, and (6) hyperacusis scores. Both lifetime noise exposure and age were the predictor variables, while the sex of participants and their cognitive function as reflected by the forward and backward digit span scores were considered covariates.

All analyses followed the pre-registered protocol. However, to address the potential concern that participants with no reported

noise exposure could exert undue influence on the statistical models, all analyses using lifetime noise exposure scores were re-run with these participants excluded. These additional analyses are reported in **Supplementary Material**.

RESULTS

Lifetime Noise Exposure

Figure 1 illustrates the distribution of lifetime noise exposure in both age groups. Lifetime noise exposure scores were spread similarly across the two age groups. Since lifetime noise exposure scores were not normally distributed in both the young and older groups as found by the Kolmogorov–Smirnov test ($p < 0.05$), a Wilcoxon-Mann-Whitney test was used to compare the means of lifetime noise exposure across the two age groups. Lifetime noise exposure scores of the young group (median = 0.02, inter-quartile range = 1.73) were statistically similar to those of the older group (median = 0.32, inter-quartile range = 2.0; $U = 9410$, $p = 0.142$).

Speech Perception in Noise

The Effect of Lifetime Noise Exposure

Figure 2 illustrates SPiN thresholds as a function of lifetime noise exposure (expressed in logarithmic units). The primary linear regression model showed that the DIN thresholds in the older group did not vary significantly as a function of lifetime noise exposure [$R^2 = 0.064$, $F_{(4,42)} = 0.71$, $p = 0.337$]. The covariates of sex and cognitive ability (as reflected by the forward and backward digit span scores) were not significant predictors of the DIN thresholds in the older group. The exploratory multiple linear regression models showed that lifetime noise exposure did not predict the DIN thresholds in the young group [$R^2 = 0.077$, $F_{(4,89)} = 1.85$, $p = 0.508$]; the CRM thresholds in the older group [$R^2 = 0.072$, $F_{(4,\ 42)} = 0.815$, $p = 0.852$]; nor the CRM thresholds in the young group [$R^2 = 0.142$, $F_{(4,89)} = 3.68$, $p = 0.237$]. Neither sex nor cognitive function were significant predictors.

The Effect of Age

Figure 3 shows the DIN and CRM thresholds among participants with low lifetime noise exposure in the young and older groups. The primary linear regression model showed that the DIN thresholds were significantly higher among the low-noise older participants (mean = −10.58 dB, $SD = 1.34$ dB) compared to their young low-noise counterparts [mean = −11.26 dB, $SD = 1.15$ dB; $R^2 = 0.083$, $F_{(4,\ 108)} = 2.45$, $p = 0.006$]. Neither the sex of participants nor their cognitive function were significant predictors of DIN thresholds in the regression model. The exploratory regression model for the effect of age on CRM threshold showed that low-noise older participants performed significantly worse (i.e., higher thresholds; mean = −5.15 dB, $SD = 5.81$ dB) than their young low-noise counterparts [mean = −9.63 dB, $SD = 5.64$ dB; $R^2 = 0.169$, $F_{(4,\ 108)} = 5.49$, $p = 0.001$]. Neither sex nor cognitive function were significant predictors.

Self-Reported Hearing Ability

The Effect of Lifetime Noise Exposure

Figure 4 illustrates the SSQ12 scores as a function of lifetime noise exposure. For the primary linear regression model for the older group, the SSQ12 scores did not vary significantly as a function of lifetime noise exposure [$R^2 = 0.059$, $F_{(4,72)} = 1.12$, $p = 0.06$]. Neither sex nor cognitive function were significant predictors. For the young group, the exploratory regression model showed that lifetime noise exposure did not predict the SSQ12 scores [$R^2 = 0.04$, $F_{(4,212)} = 2.21$, $p = 0.104$]. Neither sex nor cognitive function were significant predictors.

The Effect of Age

Figure 5A shows the SSQ12 scores among low-noise participants in the young and older groups. As per the primary linear regression model, older low-noise participants had similar SSQ12 scores (mean = 7.43, $SD = 1.64$ dB) compared to their low-noise young counterparts (mean = 7.72, $SD = 1.32$) [$R^2 = 0.03$, $F_{(4,\ 225)} = 1.76$, $p = 0.787$]. Neither sex nor cognitive function were significant predictors.

Tinnitus

The Effect of Lifetime Noise Exposure

Figure 6 shows the distribution of lifetime noise exposure scores as a function of the presence of tinnitus. The primary logistic regression model showed that lifetime noise exposure did not predict the number of participants with tinnitus in the older group (OR = 1.11, 95%CI = 0.81–1.15, $p = 0.516$). These logistic regressions are also reported in **Supplementary Material**, excluding participants with no noise exposure. Neither sex nor cognitive function were significant predictors. The exploratory logistic regression model for the young group showed that more participants reported tinnitus as their lifetime noise exposure increased (OR = 1.50, 95%CI = 1.13–1.99, $p = 0.005$). Neither sex nor cognitive function were significant predictors.

Figure 7 shows the THI scores reported by participants with tinnitus as a function of lifetime noise exposure. Exploratory linear regression models showed that lifetime noise exposure did not predict the THI scores in the young [$R^2 = 0.05$, $F_{(4,35)} = 0.49$, $p = 0.307$] nor older [$R^2 = 0.09$, $F_{(4,\ 21)} = 0.49$, $p = 0.461$] groups. Neither sex nor cognitive function were significant predictors.

The Effect of Age

Figure 5C illustrates the number of participants with low lifetime noise exposure who reported tinnitus. For the primary logistic regression model, the proportion of low-noise participants with tinnitus was significantly higher in the older than in the young group (OR = 2.64, 95%CI = 1.29–5.38, $p = 0.008$). Neither sex nor cognitive function were significant predictors.

Figure 5D shows the distribution of THI scores across low-noise participants who reported tinnitus in the young and older groups. The exploratory regression models showed that the THI scores were similar across low-noise participants in the young (mean = 10.57, $SD = 8.76$) and older (mean = 12.44, $SD = 10.55$)

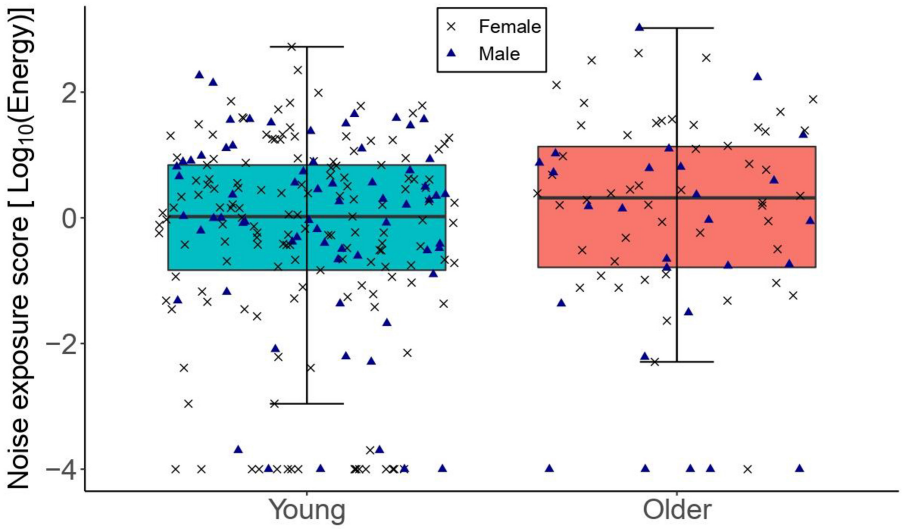

FIGURE 1 | The distribution of lifetime noise exposure for the young (n = 217) and older (n = 78) groups. The left-hand side boxplot corresponds to the older group, while the right-hand side boxplot corresponds to the young group. The upper and lower hinges boxes represent the first and the third quartiles, the thick line the median, the upper whiskers the highest value within 1.5 * IQR (interquartile range) of the upper hinge, and lower whiskers the lowest value within 1.5 * IQR of the lower hinge. Black crosses and blue triangles correspond to individual female and male participants, respectively.

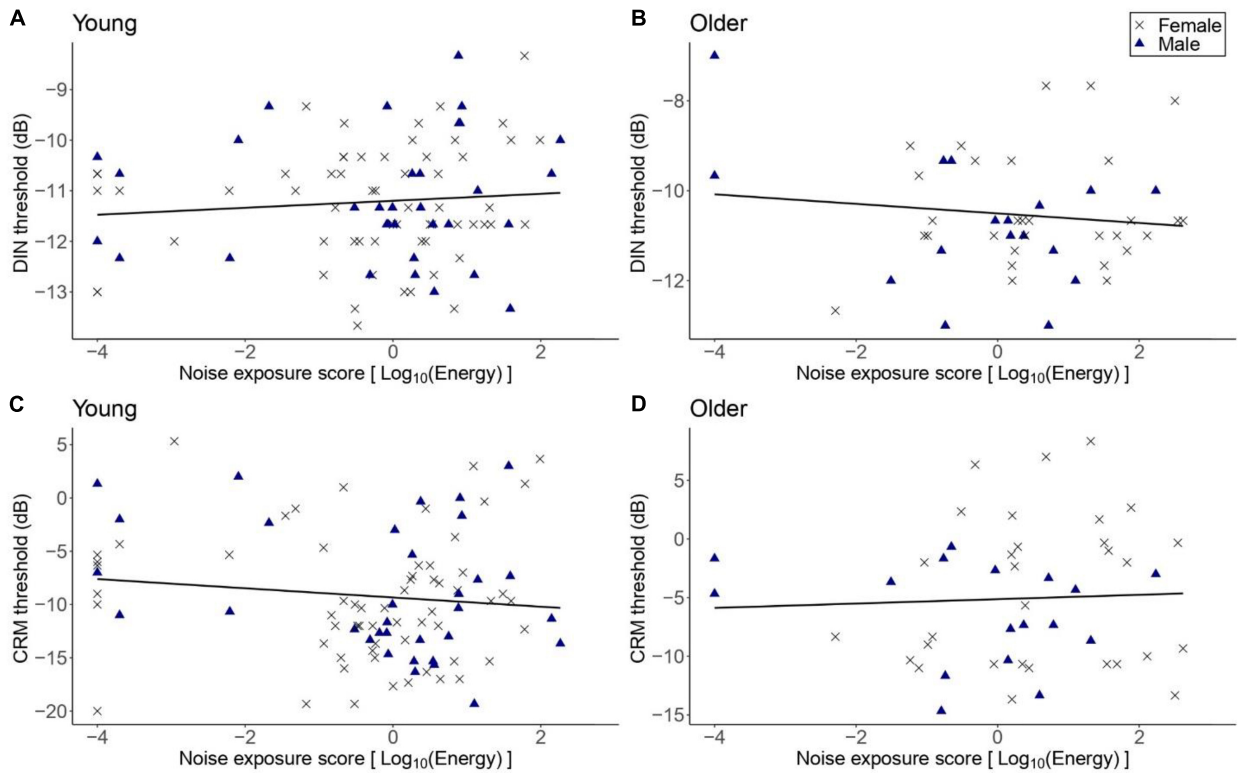

FIGURE 2 | DIN and CRM thresholds as a function of lifetime noise exposure. **(A,B)** DIN and thresholds in the young (n = 94) and older (n = 47) groups, respectively. **(C,D)** CRM thresholds in the young and older groups, respectively. Black crosses and blue triangles represent individual female and male participants, respectively. Best-fit regression lines are drawn through the data points.

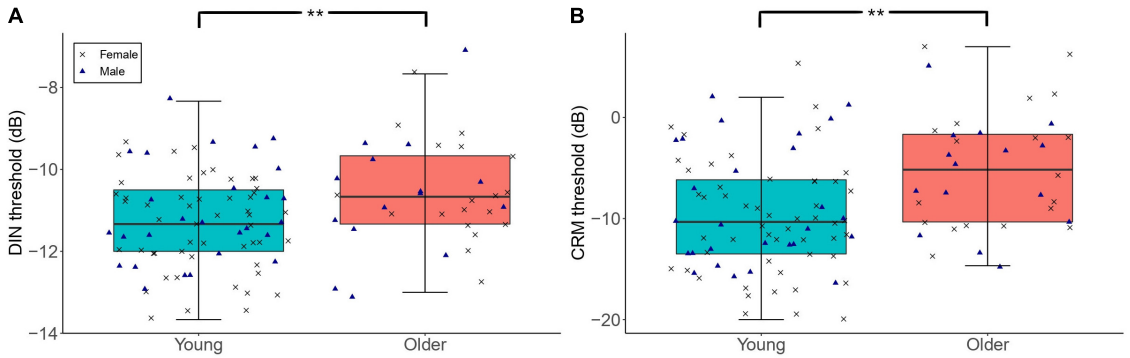

FIGURE 3 | The distribution of DIN **(A)** and CRM **(B)** thresholds among participants with low lifetime noise exposure (<1.0 logarithmic units) in the young (n = 79) and older (n = 34) groups. For each of the panels, the left-hand side boxplot corresponds to the older group, while the right-hand side boxplot corresponds to the young group. The upper and lower hinges boxes represent the first and the third quartiles, the thick line the median, the upper whiskers the highest value within 1.5 * IQR (interquartile range) of the upper hinge, and lower whiskers the lowest value within 1.5 * IQR of the lower hinge. Black crosses and blue triangles correspond to individual female and male participants, respectively. ** Represent statistical outcomes with significance level < 0.01.

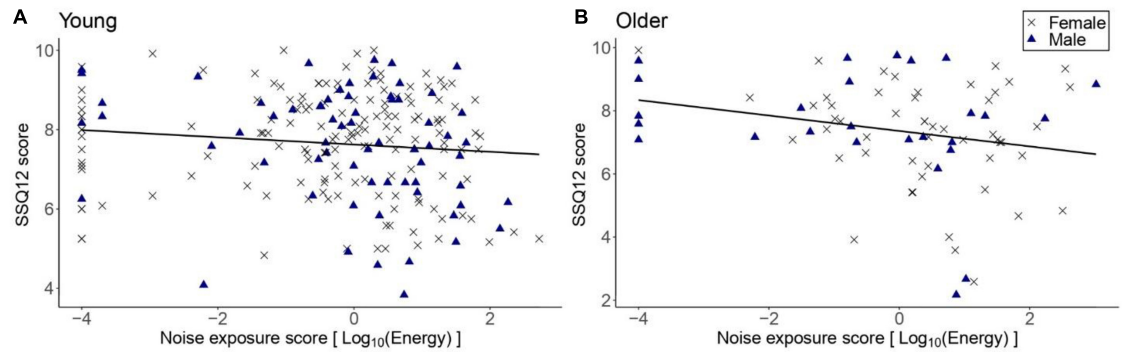

FIGURE 4 | SSQ12 scores as a function of lifetime noise exposure expressed in logarithmic scale. **(A)** corresponds to the data of the young group (n = 217) while **(B)** to the older group (n = 78). Black crosses and blue triangles represent individual female and male participants, respectively. Best-fit regression lines are drawn through the data points.

groups [R^2 = 0.04, $F_{(4,\ 44)}$ = 0.40, p = 0.448]. Neither sex nor cognitive function were significant predictors.

Hyperacusis

The Effect of Lifetime Noise Exposure

Figure 8 shows the hyperacusis scores as a function of lifetime noise exposure. The exploratory linear regression models showed that hyperacusis scores in the young group were significantly higher as lifetime noise exposure increased [R^2 = 0.05, $F_{(4,212)}$ = 2.81, p = 0.001]. For the older group, lifetime noise exposure did not predict hyperacusis scores [R^2 = 0.049, $F_{(4,72)}$ = 0.93, p = 0.812]. Neither sex nor cognitive function were significant predictors in either model.

The Effect of Age

Figure 5B shows the distribution of hyperacusis scores among low-noise participants in both age groups. The exploratory linear regression model showed that the hyperacusis scores of low-noise young participants (mean = 0.78, SD = 0.50) did not differ significantly from those of their older counterparts [mean = 0.82, SD = 0.55; R^2 = 0.006, $F_{(4,225)}$ = 0.33, p = 0.611]. Neither sex nor cognitive function were significant predictors.

The Interaction Between Lifetime Noise Exposure and Age

In further exploratory analyses, lifetime noise exposure, age group (i.e., young and older), and an interaction term (lifetime noise exposure × age group) were included as predictors in the model for each outcome variable, with covariates of sex and cognitive function. Main effects of (1) age group on DIN thresholds [adjusted R^2 = 0.13, $F_{(1)}$ = 10.25, p = 0.013], (2) lifetime noise exposure on hyperacusis scores [adjusted R^2 = 0.44, $F_{(252)}$ = 1.88, p = 0.019], and (3) age group on the proportion of subjects with tinnitus (beta = −0.088, p = 0.004) were observed. The interaction between lifetime noise exposure and age group was significant for hyperacusis scores only [$F_{(1,\ 252)}$ = 2.66, p = 0.034, $\eta^2\rho$ = 0.34) such that the effect of noise exposure on hyperacusis scores was smaller for the older group compared to the young. No other effects were significant.

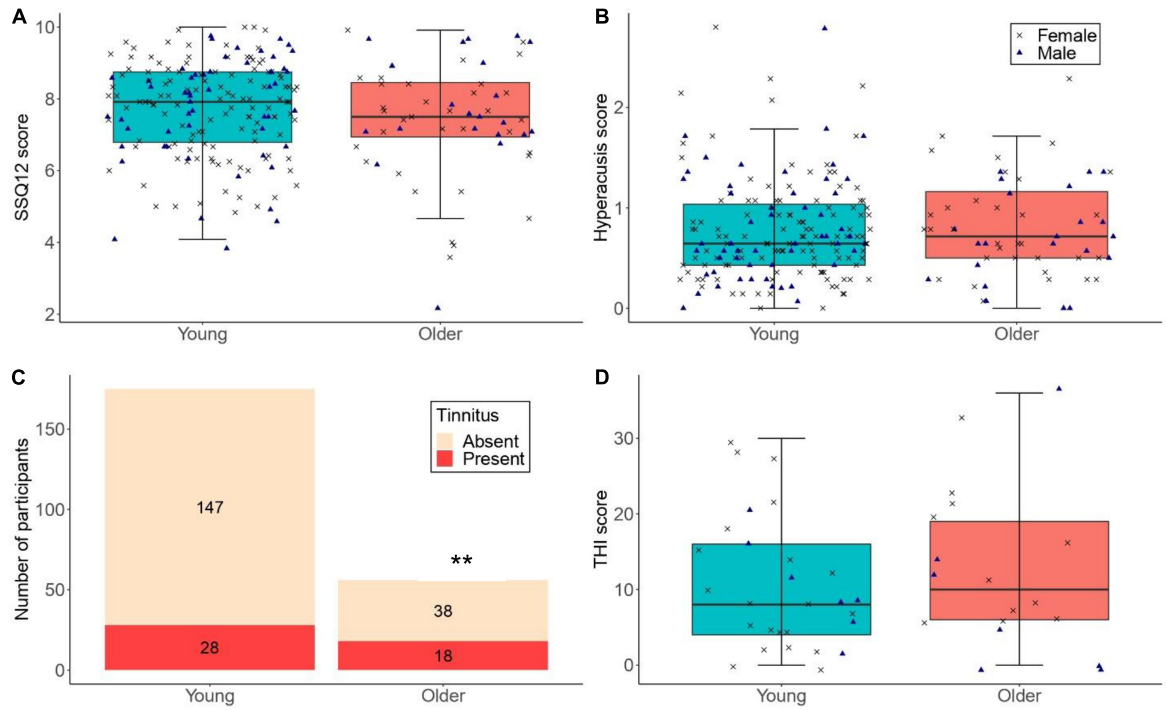

FIGURE 5 | (A,B) The distribution of SSQ12 scores and hyperacusis scores for participants with low lifetime noise exposure (<1.0 logarithmic units) in the young (n = 175) and older (n = 56) groups. **(C)** The number of low-noise participants who reported tinnitus in the young (n = 175; proportion of low-noise participants with tinnitus in the young group = 16.0%) and older (n = 56; proportion of low-noise participants with tinnitus in the older group = 32.1%) groups (** denotes $p < 0.01$). **(D)** THI scores for low-noise participants who reported tinnitus in the young (n = 28) and older (n = 18) groups. For **(A,B,D)**, the left-hand side boxplot corresponds to the young group, while the right-hand side boxplot corresponds to the older group. The upper and lower hinges represent the first and the third quartiles, the thick line the median, the upper whiskers the highest value within 1.5 * IQR (interquartile range) of the upper hinge, and lower whiskers the lowest value within 1.5 * IQR of the lower hinge. Black crosses and blue triangles correspond to individual female and male participants, respectively.

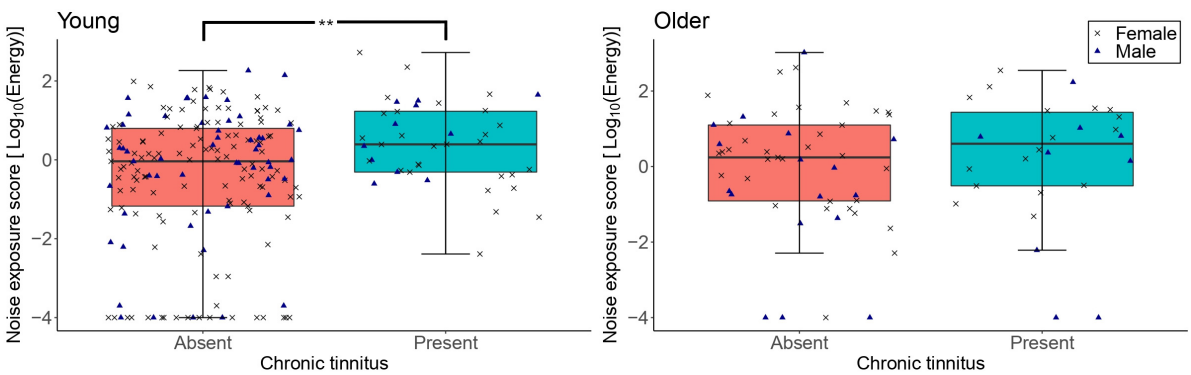

FIGURE 6 | The distribution of lifetime noise exposure scores in the young (n = 217; left-hand-side panel) and the older (n = 78; right-hand-side panel) groups as a function of the presence of tinnitus. For each of the panels, the left-hand side boxplot corresponds to absent tinnitus, while the right-hand side boxplot corresponds to present tinnitus. The upper and lower hinges represent the first and the third quartiles, the thick line the median, the upper whiskers the highest value with 1.5 * IQR (interquartile range), and lower whiskers the lowest value within 1.5 * IQR of the lower hinge. Black crosses and blue triangles correspond to individual female and male participants, respectively. ** denotes $p < 0.01$.

DISCUSSION

We hypothesized that higher lifetime noise exposure in the older group and age (independent of noise exposure) are associated with (i) higher SPiN thresholds using the DIN test, (ii) lower SSQ12 self-reported hearing scores, and (iii) a higher proportion of participants with tinnitus. In the older group, no significant effects of lifetime noise exposure on any of our primary outcome measures were found. Older low-noise participants exhibited significantly higher DIN thresholds and a higher proportion of

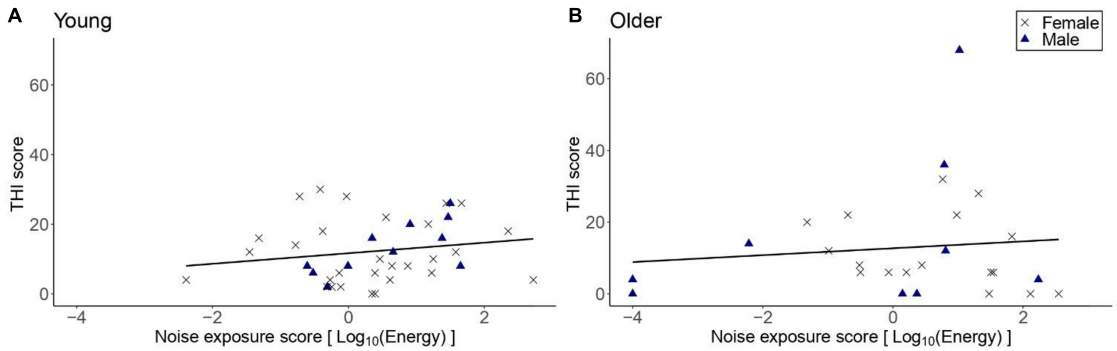

FIGURE 7 | THI scores as a function of lifetime noise exposure, for those participants who reported tinnitus. **(A)** Shows the data for the young group (n = 40) while **(B)** the data for the older group (n = 26). Black crosses and blue triangles represent individual female and male participants, respectively. Best-fit regression lines are drawn through the data points.

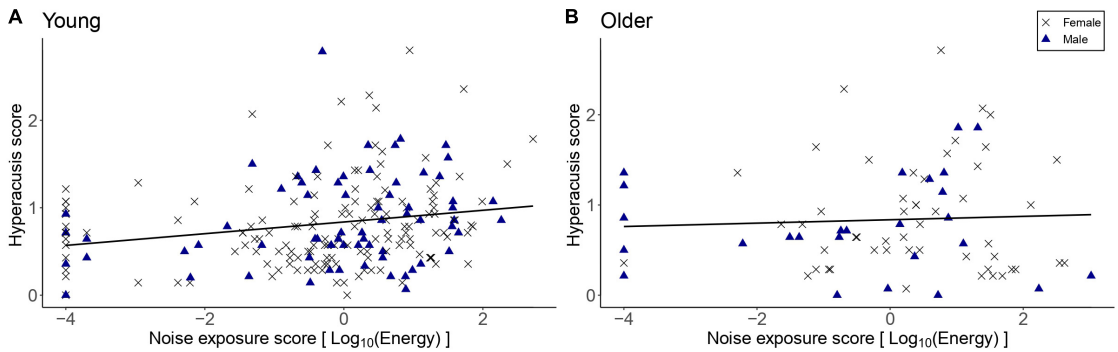

FIGURE 8 | Hyperacusis scores as a function of lifetime noise exposure for the young group (n = 217; **A**) and the older group (n = 78; **B**). Black crosses and blue triangles represent individual female and male participants, respectively. Best-fit regression lines are drawn through the data points.

tinnitus than their young counterparts. Both young and older low-noise participants had similar scores on the SSQ12.

In our exploratory analyses, we examined the effects of lifetime noise exposure in the young group and age (independent of noise exposure) on (i) CRM SPiN thresholds, (ii) the number of participants with tinnitus, (iii) tinnitus handicap severity (of participants with tinnitus), and (iv) the severity of hyperacusis. In the young group, higher lifetime noise exposure was associated with a significantly greater proportion of participants with tinnitus and higher hyperacusis scores. It should be noted that there were a greater number of younger participants than older participants and so it is possible that the effect persists in the older group, but that our study had insufficient power to demonstrate it. Lifetime noise exposure did not predict performance on the CRM task. Older low-noise participants exhibited significantly higher CRM thresholds but similar hyperacusis scores compared to their young low-noise counterparts.

Speech Perception in Noise

The Effect of Noise Exposure on Speech-Perception-in-Noise

SPiN thresholds obtained by both the DIN and CRM tests were similar across various lifetime noise exposure magnitudes in both the young and older groups. Although we expected differences in SPiN thresholds due to lifetime noise exposure which could potentially damage the inner ear structures which play a role in the audibility (i.e., outer hair cells) and intelligibility (i.e., inner hair cells and cochlear synapses) of speech signals at moderately loud suprathreshold levels, these findings are in line with several past studies which failed to document an effect of noise exposure on SPiN performance among normal-hearing young (Grose et al., 2017; Prendergast et al., 2017b; Yeend et al., 2017; Guest et al., 2018b; Couth et al., 2020) and older adults (Valderrama et al., 2018; Prendergast et al., 2019; Carcagno and Plack, 2021).

These negative findings could be explained by two different scenarios. First, the magnitude of cumulative lifetime noise to which participants in this study have been exposed may not have been sufficient to induce widespread hair cell and synapse loss which would translate into noticeable SPiN differences. A higher magnitude of lifetime noise exposure may therefore be necessary to induce significant SPiN effects. Moreover, it is possible that noise-induced CS may not preferentially result in degraded low- and medium- spontaneous rate ANFs, which in humans are thought to exhibit high thresholds (based on animal data) and thus code moderate-to-high acoustic information such as speech (Liberman, 1978; Furman et al., 2013). In the absence of single-unit recordings in humans, it is impossible to confirm the

thresholds of ANFs lost due to noise exposure. Additionally, the effects of CS on speech perception may be insignificant compared to those of a wide array of cognitive, linguistic, and attentional factors, leaving day-to-day perception largely unaffected. Thus, the assumption that noise-induced CS results in SPiN difficulties is still under debate (Hickox et al., 2017; Le Prell, 2019).

Second, the tools used in this study may lack sufficient sensitivity to detect the hypothesized effects. For instance, it is possible that a limited noise-induced synapse loss has already occurred with minimal outer hair cell loss, however, the current DIN task may not be sufficiently sensitive to show the differences in SPiN performance. According to Oxenham (2016), a synapse loss of up to 50% in humans may not necessarily be detectable using behavioral tasks. Moreover, the currently employed method to quantify noise exposure (i.e., self-reported questionnaire) may not be reliable as it is primarily based on participants' ability to recall instances of intense acoustic over-exposure throughout the lifespan.

The Effect of Age on Speech-Perception-in-Noise

SPiN hearing thresholds using both the DIN and CRM tasks were significantly higher among low-noise older participants compared to their young counterparts. These findings imply a clear age-related effect on SPiN ability and are generally consistent with several past studies (Pichora-Fuller et al., 1995; Kim et al., 2006; Füllgrabe et al., 2015; Babkoff and Fostick, 2017; Johannesen et al., 2019; Patro et al., 2021).

Prendergast et al. (2019) reported worse SPiN performance among older participants using the DIN task using the 80 dB SPL stimulus condition (but not the 40 dB SPL condition). In contrast, Carcagno and Plack (2021) failed to document such an effect using the DIN test which involved pink band-pass filtered noise at 3–8 kHz and low-pass filtered speech stimuli with a cut-off at 3 kHz presented at low and high levels. For the CRM test, neither Prendergast et al. (2019) nor Carcagno and Plack (2021) found credible age-related differences in the CRM thresholds at either stimulus level.

Several factors may have contributed to the age-related effects on SPiN ability as seen in the current study. First, since this study was conducted entirely online, it was not possible to measure and control for age-related audiometric threshold elevation both within the standard and the extended audiometric ranges (which is primarily driven by ARHL). Age-related outer hair cell loss within the standard audiometric range may compromise SPiN performance (Hoben et al., 2017; Keithley, 2020). Moreover, the elevation in extended high-frequency thresholds, which is common at an older age (Valiente et al., 2014; Wang et al., 2021), has been associated with worse SPiN performance (Monson et al., 2019; Yeend et al., 2019; Zadeh et al., 2019; Hunter et al., 2020).

Second, although we attempted to control for age-related cognitive decline, which can result in poorer SPiN performance (Humes and Dubno, 2009; Kamerer et al., 2019), poorer central auditory processing, which is typically associated with aging, could account for the observed SPiN differences (Caspary et al., 2008; Ouda et al., 2015). Interestingly, the age-related difference using the CRM task was much greater than that obtained by the DIN test. This could be due to the involvement of central factors since the CRM task is more complex than the DIN test and hence may place greater demands on cognitive factors (Heinrich et al., 2015). Third, given the inability to isolate the effects of outer hair cell loss and central auditory processing in the current study, it is impossible to rule out the contribution of age-related CS and ANF loss to the poorer SPiN performance in the older group as recent human temporal bone data provided compelling evidence in support of age-related CS and ANF degeneration (Viana et al., 2015; Wu et al., 2019, 2021).

Self-Reported Hearing Ability

The Effect of Noise Exposure on the Speech Spatial and Qualities of Hearing Questionnaire

Self-reported hearing ability, as assessed by the SSQ12 questionnaire, did not vary significantly as a function of lifetime noise exposure in the young or the older groups. It is worth pointing out that participants in the older group with higher noise exposures tended to have the worse self-reported hearing ability, but the effect was non-significant even before correction for multiple comparisons ($p = 0.06$). These negative findings were similar to those of other studies which investigated normal/near-normal hearing participants of various ages and failed to document poorer scores on either the full or short versions of the SSQ as a function of higher noise, such as Prendergast et al. (2017b), Yeend et al. (2017), and Carcagno and Plack (2021).

The Effect of Age on the Speech Spatial and Qualities of Hearing Questionnaire

Young low-noise participants produced similar SSQ12 scores to those of older low-noise participants. These findings are in line with the outcomes reported by Füllgrabe et al. (2015) and Carcagno and Plack (2021) who documented statistically similar performance on the SSQ12 and SSQ, respectively, across normal/near-normal hearing participants of different ages. Banh et al. (2012) showed a similar outcome to our study in that the average SSQ score of older adults with normal hearing up to 4 kHz was slightly worse (mean SSQ score = 7.7, $SD = 1.2$) than the scores obtained by younger normal-hearing adults (mean SSQ score = 8.8, $SD = 1.9$). However, older adults with moderate hearing loss had significantly worse mean SSQ scores of 5.5 than younger and older normal-hearing participants (as defined by normal hearing thresholds up to 4 kHz).

The lack of significant effects of lifetime noise exposure and age on SSQ12 scores in the current study could stem, at least partially, from the possibility that most of our participants may have had normal/near-normal low- and mid-frequency hearing thresholds. Thus, the effects of self-reported hearing difficulties may be largely unaffected by high-frequency hearing losses which typically are associated with excessive noise exposure and ARHL. Moreover, the SSQ12 may lack sufficient sensitivity to detect mild hearing difficulties that may result from excessive lifetime noise exposure and aging. Finally, Füllgrabe et al. (2015) argued that, due to social and cultural factors, older adults may tend to underestimate the effects of their hearing difficulties, which hence would reduce the efficacy of using self-reported questionnaires to highlight age-related hearing difficulties.

Tinnitus

The Effect of Lifetime Noise Exposure on Tinnitus

As lifetime noise exposure increased, a higher proportion of participants reported tinnitus in the young, but not in the older group. Consistent with these findings, Guest et al. (2017) showed that young normal-hearing adults with tinnitus reported significantly higher noise exposure compared to a non-tinnitus audiometrically-matched control group. Other studies, which did not perform audiometric matching between tinnitus and non-tinnitus normal-hearing young participants, also reported a significant association between recreational noise exposure and tinnitus (Meyer-Bisch, 1996; Davis et al., 1998; Degeest et al., 2014). Hearing threshold elevation secondary to noise-induced hearing loss (which is primarily characterized by OHC loss) is a well-established risk factor for tinnitus (Boger et al., 2016; Paulin et al., 2016). Moreover, noise-induced ANF loss (without hair cell loss) may be associated with increased compensatory central neural activity at the level of the mid-brain, which in humans is hypothesized to translate into tinnitus (Schaette and McAlpine, 2011; Hickox and Liberman, 2014). So, the central compensatory gain theory may at least partially explain the current findings, alongside potential hair cell loss. Schaette and McAlpine (2011) framed cochlear synaptopathy and the central compensatory gain mechanism as being potentially linked, though other processes could account for their observed data. Indeed, it is important to note that there are many other proposed mechanisms of tinnitus, such as lateral inhibition (Gerken, 1996), the central noise model (Zeng, 2013), and the stochastic resonance model (Schilling et al., 2021). It is not clear how completely the central compensatory gain theory can account for all instances of tinnitus, and it is not clear how compatible the other models are with a loss of cochlear synapses.

Although we expected to see a higher proportion of participants with tinnitus as a function of lifetime noise exposure in the older group, our current findings failed to establish such a link. Similar to these outcomes, Valderrama et al. (2018) found no significant difference in lifetime noise exposure between tinnitus and non-tinnitus middle-aged normal/near-normal hearing participants. An earlier study by Sindhusake et al. (2003) showed that self-reported occupational noise exposure among older adults (aged 55+) significantly increased the relative risk of tinnitus. This study, however, found that other factors such as age-related audiometric threshold elevations and other otologic pathologies were also associated with tinnitus at an older age. Thus, based on these findings, it is difficult to establish whether tinnitus may occur in the older population as a consequence of acoustic overexposure while hearing thresholds are still within the normal/near-normal audiometric range.

A prospective 10-year cohort study that documented the incidence and risk factors of tinnitus in middle-aged and older adults found that occupational, recreational, and firearm noise exposure were not associated with a higher incidence of tinnitus (Nondahl et al., 2010). Authors attributed the lack of association to the possible decrease in the frequency and magnitude of noise exposure at older ages compared to the younger population, which may be more involved in loud and noisy recreational and occupational events.

Our exploratory analyses showed that higher lifetime noise exposure was not associated with higher tinnitus handicap in either age group. It is possible that these secondary analyses lacked sufficient statistical power to detect the hypothesized effects of noise exposure on tinnitus severity which was documented by a few studies (Tong and Yeung, 2017; Bhatt, 2018). However, it is worth highlighting that, in line with our findings, House et al. (2018) reported that THI scores were not predicted by noise exposure. Further research is therefore necessary to establish the effect of noise exposure on the severity of tinnitus handicap in different age groups.

The Effect of Age on Tinnitus

In the current study, we found a significantly higher proportion of participants with tinnitus among low-noise older participants compared to their young low-noise counterparts. This implies that aging, which is typically associated with peripheral and central auditory degeneration, may increase the risk of tinnitus.

A higher risk of tinnitus at an older age is well-established across the literature (Ahmad and Seidman, 2004; Nondahl et al., 2010; Shargorodsky et al., 2010; Kim et al., 2015; McCormack et al., 2016). This age-related increase in the risk of tinnitus is often attributed to ARHL, otologic pathologies, head and neck traumas, neurological disorders, and other lifestyle factors such as smoking and alcohol consumption (Ahmad and Seidman, 2004; Shargorodsky et al., 2010; Kim et al., 2015). In the current study, while we attempted to control for factors such as lifetime noise exposure, sex of participants, otologic pathologies, head and heck traumas, past diagnosis of hearing impairment, cognitive function, and intake of ototoxic medications, we cannot rule out the contribution of undiagnosed age-related threshold elevation to the higher proportion of participants of tinnitus in the older group. This is because the presence of high-frequency hearing impairment, which typically results from age-related outer hair cell loss in basal cochlear regions, is associated with an increase in the risk of tinnitus in the older population (König et al., 2006; Terao et al., 2011).

After examining the THI scores of the participants with tinnitus as a function of lifetime noise exposure in the young and the older groups, and across low-noise participants in both age groups, neither lifetime noise exposure nor age predicted the THI scores. THI scores corresponded to the slight tinnitus handicap category across most participants in both age groups, which indicates that tinnitus is only noticeable in quiet and has no impact on sleep and daily activities (McCombe et al., 2001).

Given the exploratory nature of these analyses and the fact that the number of participants was not sufficient to provide enough power to detect an effect on THI scores, it is difficult to draw firm conclusions on whether excessive lifetime noise exposure and aging result in worse tinnitus handicap. A few studies have evaluated the risk factors associated with worse tinnitus handicap as reflected by higher THI scores. These included sex (i.e., being male), psycho-emotional disorders such as depression and anxiety, noise exposure, and aging (Hiller and Goebel, 2006; Schlee et al., 2011; Milerová et al., 2013; Bhatt, 2018; House et al., 2018). However, the evidence presented by other studies challenged these associations (Pinto et al., 2010;

Figueiredo et al., 2011; Udupi et al., 2013; Frederiksen et al., 2017; Ralli et al., 2017). Further research is, therefore, necessary to determine the effects of noise exposure and aging on tinnitus handicap.

Hyperacusis

The Effect of Lifetime Noise Exposure on Hyperacusis

In our exploratory analyses, we found that greater hyperacusis scores (i.e., worse hyperacusis severity) were associated with higher lifetime noise exposure in the young group, but not in the older group. The effect found in the young group is in line with the findings of several studies which documented worse hyperacusis among young noise-exposed normal-hearing adults and adolescents (Widen and Erlandsson, 2004; Yilmaz et al., 2017; Camera et al., 2019; Couth et al., 2020; Fredriksson et al., 2021; Pienkowski, 2021). Although audiometric threshold elevation in the standard audiometric range is considered a primary initiating mechanism for hyperacusis (Knipper et al., 2013; Auerbach et al., 2014; Pienkowski et al., 2014), acoustic overexposure seems to induce worse hyperacusis in young normal-hearing adults. Noise-induced loss of ANFs in the absence of outer hair cell damage may contribute to worse hyperacusis due to increased central compensatory gain (Schaette and McAlpine, 2011; Hickox and Liberman, 2014). However, the evidence on the association between noise-induced hyperacusis and increased central gain is still inconclusive (Möhrle et al., 2019; Couth et al., 2020).

The lack of association between lifetime noise exposure and hyperacusis in the older group could be explained by the hypothesis that the effect of noise exposure on the peripheral neural auditory system at an older age could manifest differently than young age. Recent temporal bone data by Wu et al. (2021) established that lifetime occupational noise exposure produced more severe ANF loss in middle-aged but not in older adults. This is consistent with rodent data from Möhrle et al. (2016) who showed that middle-aged and older rats exhibited significantly less noise-induced synapse loss compared to their young counterparts. Thus, older adults may experience limited additional perceptual auditory effects such as tinnitus and hyperacusis due to noise exposure.

The Effect of Age on Hyperacusis

Aging, which is typically associated with cochlear hair cell and ANF loss, has been associated with the development of hyperacusis in older adults (Andersson et al., 2002; Tyler et al., 2014; Paulin et al., 2016). Other age-related comorbidities such as cardiovascular disease, psycho-emotional disorders (e.g., depression and anxiety), and neurologic conditions such as multiple sclerosis are thought to result in worse hyperacusis severity in the older population (Tyler et al., 2014). In the current study, older low-noise participants exhibited similar hyperacusis scores compared to their young low-noise counterparts. Further research, which could potentially control for age-related cochlear hair cell loss and other aging comorbidities, is necessary to disentangle the factors which increase the risk of hyperacusis at an older age.

Strengths and Limitations

The current study employed a novel approach to collect an extensive dataset of self-reported hearing and SPiN data using online instruments. These online data-collection tools enabled access to a wide demographic of participants from various social, cultural, ethnic, and educational backgrounds in the United Kingdom. Moreover, the convenience of remote online data collection allowed the researchers to carry out the current study during the COVID-19 pandemic when in-person testing was not an option. Since many of the findings of the current study are in line with previous laboratory-based studies in the literature, the current remote approach provides promise for future research studies using similar online techniques to collect large datasets, enhancing statistical power to detect hypothesized effects.

We must acknowledge several limitations of the current study. First, since the noise exposure questionnaire heavily relies on participants' ability to recall the details of past noise exposure throughout their lifespan, it is possible that participants have either under- or over-estimated their lifetime noise exposure. Second, although there may be wide variability in the lifetime noise exposure scores across participants, it is hard to ascertain whether participants with the highest noise exposure scores had sufficiently high cumulative lifetime noise exposure to produce measurable effects using the different outcome measures employed.

Third, although we tried to rule out participants with a diagnosis of hearing impairment and those with a documented history of head/neck traumas, otologic pathology, ear surgeries, and ototoxic exposure, it is likely that some participants may have had a pre-existing undiagnosed age-related hearing impairment which could have influenced the findings of the current study.

Fourth, since participants used their own headphones/earphones to conduct the online SPiN task, the different headphone/earphone brands might have produced variable sound quality/level, which could add further inter-subject variability to SPiN outcomes (though DIN stimuli were low-pass filtered below 8 kHz to exclude potential influence from the high-frequency region, where the greatest variability in transducer performance is likely to be observed). Fifth, although we instructed our participants to perform the SPiN tasks in a quiet place with minimal distractions, it is possible that some participants performed the SPiN tasks in sub-optimal acoustic conditions.

Finally, the older group was smaller than the young group. This resulted in a reduced statistical power to detect the hypothesized effects of lifetime noise exposure in the older group.

CONCLUSION

The findings of our study, which was carried out using novel online instruments, support the existing evidence that aging is associated with worse SPiN ability and other hearing-related symptoms such as tinnitus. However, the effect of noise exposure on tinnitus and hyperacusis was not consistent

across the young and older groups. For the young group only, lifetime noise exposure was associated with a higher proportion of participants reporting tinnitus and worse severity of hyperacusis. No significant effect of lifetime noise exposure on SPiN ability, self-reported hearing, nor the severity of tinnitus handicap was found in either age group. It is not clear whether the effects of noise on the peripheral auditory system are limited, or lead to limited effects on perception, or whether the currently employed self-report and behavioral SPiN tools lack the sensitivity to detect these effects. Despite the potential lack of sensitivity, online studies are more convenient and easier to recruit participants than traditional lab-based studies and may be useful in future research efforts.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://osf.io/jzu4t/files/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Manchester Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.890010/full#supplementary-material

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Exploring the Association of Leukocyte Telomere Length and Hearing Threshold Shifts of Adults in the United States

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Background: Although telomere length has a significant relationship with various age-related diseases, studies on its relationship with hearing status in adults are limited and equivocal. This study investigated the associations between mean telomere length (MTL) and low-, speech-, and high-frequency hearing threshold shifts of adults in the United States.

Methods: A total of 2,027 adults, aged 20-69 years, from the National Health and Nutrition Examination Surveys (NHANES, 1999–2002) were included in the analytic sample. The quantitative polymerase chain reaction method was used for the MTL assay, and MTL was expressed using the telomere-to-single copy gene (T/S) ratio. Hearing loss was defined as a pure-tone average (PTA) for the better ear at $\geq$ 20 dB HL at frequencies 500, 1,000, 2,000, and 4,000 Hz. Univariate and multivariate linear regression analyses and smooth curve fittings were conducted to evaluate the correlation between MTL and low-, speech-, and high-frequency hearing levels.

Results: The mean age of the participants was 40.60 $\pm$ 12.76 years, including 952 men (weighted, 48.67%) and 303 (weighted, 12.88%) participants with hearing loss. After adjusting for potential confounders in the multivariate linear regression model, the relationship between MTL and hearing thresholds was not statistically significant. Smooth curve fittings indicated a non-linear relationship between MTL and high-frequency PTA hearing threshold shifts. MTL was inversely related to high-frequency PTA to the turning point (T/S ratio = 0.82) (adjusted β −21.45, 95% CI −37.28, −5.62; $P = 0.008$). When the T/S ratio exceeded0.82, MTL was not associated with high-frequency PTA (adjusted β0.18, 95% CI −2.21, 2.57; $P = 0.8809$).

Conclusion: Our findings revealed that MTL was associated with high-frequency PTA hearing threshold shifts of adults in the United States in a non-linear manner.

Keywords: telomere length, hearing threshold shift, National Health and Nutrition Examination Survey, cross-sectional study, adults

INTRODUCTION

Hearing loss, which is associated with lifelong adverse health consequences and affects social and economic development, is the most common sensory disability in humans (Bowl et al., 2017; Cunningham and Tucci, 2017). It can originate in childhood (Vos et al., 2017) and is increasingly prevalent in adults (Agrawal et al., 2008). Genetic and environmental factors can cause hearing loss. Although genetic mutations, noise exposure, ototoxic drugs, and aging are the most studied risk factors for hearing loss, understanding of the underlying biological and molecular mechanisms of hearing loss is still limited.

Telomeres are repetitive DNA sequences (TTAGGG in vertebrates) and associated proteins at the ends of chromosomes for chromosomal stability and cellular integrity (Blackburn et al., 2015). They are considered biomarkers of aging because they shorten with every cell division (Chakravarti et al., 2021). Many age-associated diseases and disorders, such as hypertension, cognitive performance disorder, and cancer mortality, have been studied (Huang et al., 2020; Linghui et al., 2020; Shen et al., 2020). Oxidative stress and inflammation, which can promote hearing loss, are associated with telomere loss (von Zglinicki et al., 2001; Chester et al., 2021; Heba et al., 2021). Thus, telomere length may predispose hearing status and telomere loss may be associated with the biological mechanisms of hearing loss.

To date, the results of studies on the relationship between telomere length and hearing level are quite limited and inconsistent (Liu H. et al., 2017; Wang et al., 2019; Zhang et al., 2020). One study showed that longer telomere length was negatively related to hearing loss in older adults (Liu H. et al., 2017). In another study, telomere length was considered a predictive biomarker of hearing loss at an early stage (Zhang et al., 2020). However, telomere length was not correlated with hearing levels in children and midlife adults in a third study (Wang et al., 2019). Therefore, this study investigated the relationship between mean telomere length (MTL) and hearing level of adults in the United States using the National Health and Nutrition Examination Survey (NHANES) database.

MATERIALS AND METHODS

Ethics Statement

Our study acquired publicly accessible data from the NHANES website[1]. The NHANES data were approved by the National Center for Health Statistics Institutional Review Board by the revised Declaration of Helsinki. Data collection procedures and examinations were performed after informed consent was obtained from all the eligible participants.

Study Population

The NHANES is a nationally representative survey approved by the Institutional Review Board of the National Center for Health Statistics. The survey combines a series of interviews, physical examinations, and laboratory tests to collect health-related information from the general population in the United States. The population in this study was enrolled in two cycles of NHANES (1999—2000, 2001–2002), as these are the only cycles containing results of the leukocyte telomere length test. A flow chart for the selection of study participants is shown in **Figure 1**. Audiometry examinations were performed in adults aged 20–69 years. Participants without complete data on hearing levels, otoscopic test, tympanogram test, or leukocyte telomere length measurement were excluded, as well as participants with abnormal otoscopic results, poor-quality tympanogram results, or tympanogram with compliance of $\leq$ 0.3ml. Finally, 2,027 adults were included in the study.

Leukocyte Telomere Length Measurement

DNA from the participants was purified from whole blood and stored at −80°C using standardized procedures before the MTL assay measurement. The MTL assay was performed in the laboratory at the University of California, San Francisco, using the quantitative polymerase chain reaction-based method to measure telomere length relative to standard reference DNA (telomere-to-single copy gene [T/S] ratio), as previously described in detail (Cawthon, 2002; Lin et al., 2010; Needham et al., 2013). More details regarding the MTL quantification procedure and analytical methods are available on the NHANES website[2].

Audiometric Measurement

Standardized air conduction pure-tone audiometric measurements were conducted in a sound-isolated room by trained and certificated audiologists. Air-conduction thresholds were tested in both ears of the participants at frequencies between 500 and 8,000 Hz, each with an intensity range of −10 to 120 dB. The hearing threshold was defined as the level at which participants were able to detect 50% of the signal. The 1,000 Hz frequency was tested twice in each ear to ensure quality and reliability (Su and Chan, 2017). Pure-tone average (PTA) hearing thresholds were regarded as: 0.5, 1, and 2 kHz low-frequency; 0.5, 1, 2, and 4 kHz speech-frequency; 4, 6, and 8 kHz high-frequency. Hearing impairment was defined as a hearing threshold of 20 dB or greater at speech-frequency PTA in the better ear (World Health Organization [WHO], 2021).

Covariates

Potential covariates considered in the analyses included age, body mass index (BMI), sex, race/ethnicity, education level, diabetes, hypertension, cigarette smoking, and noise exposure. Information on age, sex, race/ethnicity, education level, diabetes, and hypertension were obtained during the in-home interviews. Information on noise exposure was obtained from a pre-exam

[1]https://www.cdc.gov/nchs/nhanes/Index.htm

[2]https://wwwn.cdc.gov/nchs/nhanes/1999-2000/telo_a.htm

audiometric questionnaire. BMI data were recorded during the physical examination.

Diabetes was determined if the participants answered responded 'yes' to "other than during pregnancy, ever been told by a doctor or health professional had diabetes or sugar diabetes." The answer of "borderline" was also considered diabetes (Szeto et al., 2021). Hypertension was determined by a positive reply to "ever been told by a doctor or other health professional had hypertension, also called high blood pressure" (Szeto et al., 2021). Smoking status was categorized as "ever" or "never" from the answers to the questions, "Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes?" (Szeto et al., 2021). Noise exposure was defined as "exposed to loud noise or listening to music with headphones in the past 24 h" (Ding and Park, 2020).

Statistical Analysis

The 1999/2000 and 2001/2002 cycles were combined, and audiometry subsample of 4-year Mobile Examination Center weights (WTSAU4YR) of the two cycles were used to estimate more representative measures for the general population of the United States following the NHANES analytic guidelines (Zipf et al., 2013). Categorical data are shown as percentages and continuous data are presented as means ± standard deviation (SD) according to baseline MTL in quartiles (**Table 1**). The *P-value* of continuous data was calculated by the weighted linear regression model and the *P-value* of categorical data was calculated by the weighted chi-square test. A univariate analysis was conducted to estimate potential variables (**Table 2**). A multivariate linear regression analysis was used to determine regression coefficients (β) and 95% confidence intervals (CIs) between MTL and low-, speech-, and high-frequency PTAs (**Table 3**). Three regression models were built to adjust for the relevant covariates. In the crude mode, no adjustments were included. In the model I, we adjusted for sex and age. In model II, sex, age, race, education level, BMI, noise exposure, hypertension, diabetes, and cigarette smoking status were adjusted. The βs and 95% CIs of low-, speech-, and high-frequency PTAs across each MTL/age, MTL/sex, and MTL/race subgroup were analyzed and their interactions were estimated. Smooth curve fittings were used to explore the relationship between MTL and hearing threshold shifts, with an adjustment for potential confounders (**Figure 2**). A two piecewise linear regression model was then conducted to examine the threshold effect of MTL on hearing threshold shifts in terms of the smoothing plot. The log-likelihood ratio test was performed to determine whether a threshold existed. The inflection point was calculated using the recursive method, and the maximum model likelihood was used. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using the R statistical programming language 3.6.1 (R Foundation for Statistical Computing), and EmpowerStats software (X&Y Solutions, Inc.).

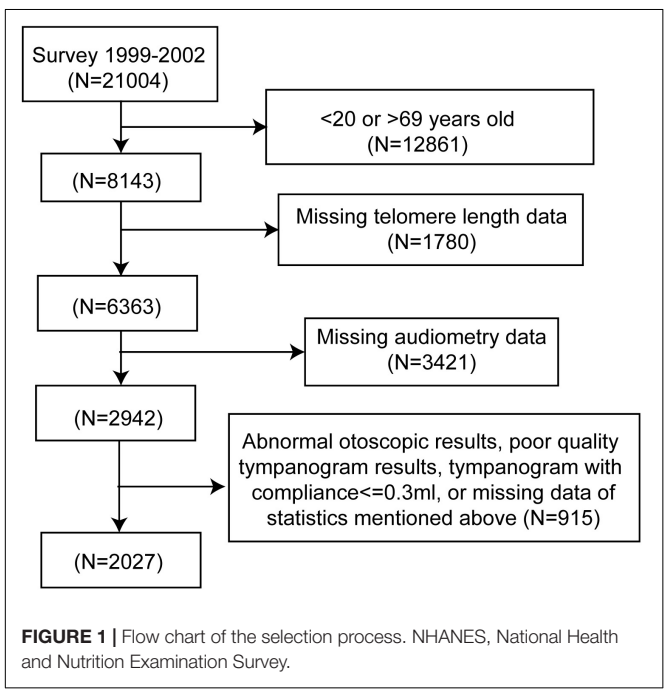

FIGURE 1 | Flow chart of the selection process. NHANES, National Health and Nutrition Examination Survey.

RESULTS

Characteristics of Participants

The baseline characteristics of the 2,027 participants (weighted mean, aged 40.60 ± 12.76 years) enrolled in this study were stratified by quartiles for MTL and are shown in **Table 1**. This study included 952 men (weighted, 48.67%) and 1,075 women (weighted, 51.33%). Of the participants, 1,367 (weighted, 64.2%) were above normal weight, 438 (weighted, 19.59%) with hypertension, and 148 (weighted, 5.94%) with diabetes. The means ± SD of low-frequency, speech-frequency, and high-frequency PTA hearing thresholds were 8.44 ± 7.30, 10.34 ± 8.70, and 18.25 ± 16.68 dB, respectively. There were 303 (weighted, 12.88%) participants with hearing loss. In addition, there were significant subgroup differences in age, low-, speech, and high-frequency PTAs, BMI, race/ethnicity, noise exposure, hypertension, diabetes, smoking status, and hearing loss rate (all $P < 0.01$).

Relationship Between MTL and Hearing Threshold Shifts

In a univariate analysis, sex, age, education level, BMI, hypertension, diabetes, cigarette smoking, and MTL (both continuous MTL and MTL in quartiles) were significantly associated with low-, speech, and high-frequency PTA hearing thresholds (all $P < 0.01$) (**Table 2**). To further explore the association between MTL and hearing threshold shifts, a multivariate regression analysis was conducted. As shown in **Table 3**, when treating MTL as a continuous variable (per 1 T/S increment) in the non-adjusted model (crude model), MTL was significantly associated with low-frequency (β = −5.01, 95% CI: −6.19, −3.84; $P < 0.01$), speech-frequency (β = −6.90, 95% CI: −8.29, −5.51; $P < 0.01$), and high-frequency (β = −12.99, 95% CI: −15.66, −10.31;

TABLE 1 | The weighted demographic characteristics of study participants.

Variables	Total	Quantile of MTL				*P* value
		Q1 (0.471-0.892) (*n* = 507)	Q2 (0.892-1.047) (*n* = 506)	Q3 (1.047-1.232) (*n* = 507)	Q4 (1.232-2.429) (*n* = 507)	
Continuous variables, mean ± SD						
Age (year)	40.60 ± 12.76	46.25 ± 12.88	42.52 ± 12.14	38.45 ± 12.21	35.91 ± 11.43	< 0.0001
BMI (kg/m^2)	28.09 ± 6.42	28.86 ± 6.87	28.51 ± 6.54	27.67 ± 6.13	27.43 ± 6.08	0.0009
Low-frequency PTA	8.44 ± 7.30	9.89 ± 8.04	9.31 ± 7.92	8.17 ± 6.87	6.61 ± 5.84	< 0.0001
Speech-frequency PTA	10.34 ± 8.70	12.57 ± 9.64	11.46 ± 9.17	9.70 ± 8.24	7.95 ± 6.98	< 0.0001
High-frequency PTA	18.25 ± 16.68	23.00 ± 19.13	20.11 ± 16.92	16.45 ± 15.79	14.07 ± 13.37	< 0.0001
Categorical variables,%						
Sex (Female)	51.33	50.48	51.36	50.43	52.92	0.8388
Race/Ethnicity						< 0.0001
Mexican American	7.50	7.92	6.75	8.70	6.66	
Non-Hispanic White	71.19	70.07	76.11	74.22	64.54	
Non-Hispanic Black	9.11	7.65	7.78	8.15	12.58	
Other races	12.21	14.36	9.36	8.94	16.21	
Education level						0.1910
Below high school	18.07	19.95	19.44	16.74	16.41	
High school	25.34	27.02	26.09	26.07	22.45	
Above high school	56.59	53.03	54.47	57.19	61.14	
Noise exposure	8.55	3.58	9.39	10.71	10.01	0.0002
BMI (kg/m^2)						0.0191
Underweight (< 18.5)	1.55	1.39	2.09	1.14	1.57	
Normal (≥ 18.5, < 25)	33.55	26.25	32.91	36.19	37.98	
Overweight (≥ 25, < 30)	34.22	36.93	32.60	34.69	32.92	
Obesity (≥ 30)	29.98	34.48	32.06	26.98	26.98	
Not recorded	0.71	0.94	0.35	1.02	0.56	
Hypertension	19.59	24.28	22.33	16.83	15.58	0.0038
Diabetes	5.94	9.80	5.45	4.82	4.12	0.0029
Cigarette smoking						< 0.0001
Never smoker	50.16	46.98	42.15	55.45	55.39	
Former smoker	23.89	27.92	31.28	18.11	18.99	
Current smoker	25.82	25.11	26.41	26.17	25.53	
Not recorded	0.13		0.16	0.27	0.09	
Hearing loss	12.88	19.16	17.02	10.34	5.92	< 0.0001

MTL, mean telomere length; SD, standard deviation; BMI, Body Mass Index; PTA, pure tone average.

$P < 0.01$) PTA hearing threshold shifts. However, in model II, there was no association between MTL and low-frequency ($\beta = -1.12$, 95% CI: −2.22, −0.01; $P = 0.0474$), speech-frequency ($\beta = -1.20$, 95% CI: −2.40, −0.00; $P = 0.0503$), and high-frequency ($\beta = -1.09$, 95% CI: −3.27, −1.09; $P = 0.3278$) PTA hearing threshold shifts. When the lowest quartiles of MTL was the referent, multivariate linear (low-, speech-, high-frequency PTAs) regression analyses demonstrated the βs for low-frequency PTA (βs0.46, 0.46, and −0.42 from the second to the fourth quartiles, respectively; $P = 0.2938$ for trend), speech-frequency PTA (βs0.33, 0.20, and −0.43, respectively, from the second to the fourth quartiles; $P = 0.2962$ for trend) and high-frequency PTA (βs −0.05, −0.46, and −0.25, from the second to the fourth quartiles, respectively; $P = 0.6687$ for trend) in the fully adjusted model (model II). MTL showed no statistically significant relationship with hearing threshold shifts after stratification by either age, sex, or race (**Supplementary Tables 1–3**).

Analyses of a Non-linear Relationship Between MTL and Hearing Threshold Shifts

After adjusting for potential confounders, including sex, age, race, education level, BMI, noise exposure, hypertension, diabetes, and cigarette smoking, a non-linear relationship between MTL and high-frequency PTA but not low-, or speech-frequency PTAs was observed (**Figure 2**). The inflection point was calculated using a two-piecewise linear regression model in the T/S ratio for the association with low-, speech-, and high-frequency PTA hearing threshold shifts to 1.14, 1.06, and 0.82, respectively. On the left of the inflection point, the βs for low-, speech-,

TABLE 2 | The univariate analysis of comparison of variables in hearing threshold group.

Variables	N (%)/Mean ± SD	Low-frequency PTA β/OR (95% CI) *p* value	Speech-frequency PTA β/OR (95% CI) *p* value	High-frequency PTA β/OR (95% CI) *p* value
Sex (Female)	1075 (53.03%)	−0.97 (−1.61, −0.34) 0.0027	−3.54 (−4.28, −2.79) < 0.0001	−8.91 (−10.31, −7.51) < 0.0001
Age	41.24 ± 14.01	0.25 (0.23, 0.27) < 0.0001	0.37 (0.34, 0.39) < 0.0001	0.77 (0.72, 0.82) < 0.0001
Race/Ethnicity				
Mexican American	494 (24.37%)	Reference	Reference	Reference
Non-Hispanic White	986 (48.64%)	0.57 (−0.65, 1.79) 0.3570	1.18 (−0.27, 2.63) 0.1116	4.08 (1.31, 6.85) 0.0040
Non-Hispanic Black	344 (16.97%)	−0.16 (−1.72, 1.41) 0.8442	−0.41 (−2.27, 1.46) 0.6695	−1.17 (−4.73, 2.39) 0.5196
Other races	203 (10.01%)	1.59 (0.12, 3.06) 0.0347	1.39 (−0.36, 3.15) 0.1200	0.96 (−2.39, 4.31) 0.5758
Education level				
Below high school	579 (28.56%)	Reference	Reference	Reference
High school	459 (22.64%)	−2.59 (−3.56, −1.62) < 0.0001	−2.78 (−3.93, −1.62) < 0.0001	−2.58 (−4.81, −0.35) 0.0235
Above high school	989 (48.79%)	−3.15 (−3.99, −2.30) < 0.0001	−3.55 (−4.56, −2.54) < 0.0001	−4.18 (−6.13, −2.22) < 0.0001
BMI				
Underweight (< 18.5)	25 (1.23%)	Reference	Reference	Reference
Normal (≥ 18.5, < 25)	615 (30.34%)	0.73 (−1.84, 3.31) 0.5777	1.73 (−1.34, 4.80) 0.2688	4.70 (−1.20, 10.61) 0.1188
Overweight (≥ 25, < 30)	724 (35.72%)	2.63 (0.06, 5.21) 0.0452	4.55 (1.48, 7.62) 0.0037	9.96 (4.05, 15.87) 0.0010
Obesity (≥ 30)	643 (31.72%)	3.59 (1.01, 6.17) 0.0065	4.84 (1.76, 7.92) 0.0021	8.57 (2.64, 14.49) 0.0046
Not recorded	20 (0.99%)	7.15 (2.67, 11.64) 0.0018	9.92 (4.58, 15.27) 0.0003	16.55 (6.26, 26.85) 0.0016
Noise exposure	170 (8.39%)	0.52 (−0.62, 1.65) 0.3738	0.49 (−0.87, 1.84) 0.4826	−0.66 (−3.26, 1.94) 0.6185
Hypertension	438 (21.61%)	3.22 (2.43, 4.01) < 0.0001	4.15 (3.21, 5.09) < 0.0001	7.23 (5.43, 9.04) < 0.0001
Diabetes	148 (7.30%)	4.95 (3.62, 6.27) < 0.0001	6.34 (4.76, 7.92) < 0.0001	12.11 (9.08, 15.14) < 0.0001
Cigarette smoking				
Never smoker	1067 (52.64%)	Reference	Reference	Reference
Former smoker	474 (23.38%)	2.43 (1.64, 3.21) < 0.0001	4.17 (3.25, 5.10) < 0.0001	8.78 (7.01, 10.55) < 0.0001
Current smoker	483 (23.83%)	1.83 (1.06, 2.59) < 0.0001	2.17 (1.27, 3.07) < 0.0001	3.01 (1.29, 4.74) 0.0006
Not recorded	3 (0.15%)	3.38 (−5.24, 12.01) 0.4420	4.39 (−5.81, 14.58) 0.3992	4.20 (−15.28, 23.69) 0.6725
MTL (per 1T/S increment)	1.08 ± 0.27	−5.01 (−6.19, −3.84) < 0.0001	−6.90 (−8.29, −5.51) < 0.0001	−12.99 (−15.66, −10.31) < 0.0001
MTL (quartiles)				
Q1 (0.471-0.892)	507 (25.01%)	Reference	Reference	Reference
Q2 (0.891-1.047)	506 (24.96%)	−0.58 (−1.48, 0.33) 0.2114	−1.10 (−2.17, −0.03) 0.0445	−2.89 (−4.95, −0.84) 0.0059
Q3 (1.047-1.232)	507 (25.01%)	−1.72 (−2.62, −0.82) 0.0002	−2.87 (−3.94, −1.80) < 0.0001	−6.55 (−8.59, −4.50) < 0.0001
Q4 (1.232-2.429)	507 (25.01%)	−3.28 (−4.17, −2.39) < 0.0001	−4.61 (−5.67, −3.55) < 0.0001	−8.93 (−10.96, −6.90) < 0.0001

SD, standard deviation; PTA, pure tone average; OR, odds ratio; CI, confidence interval; BMI, body mass index; MTL, mean telomere length.

and high frequency PTAs were −0.79 (95% CI: −1.45, 3.02; $P = 0.4913$), 0.26 (95% CI: −2.73, 3.25; $P = 0.8661$), and −21.45 (95% CI: −37.28, −5.62; $P = 0.0080$), respectively. The corresponding effect estimates at the right of inflection point were −2.56 (95% CI: −4.41, −0.72; $P = 0.0065$), −1.88 (95% CI: −3.64, −0.13; $P = -0.0358$), and0.18 (95% CI: −2.21, 2.57; $P = 0.8809$), respectively. The high-frequency PTA decreased with the T/S ratio up to the turning point (0.82). When the T/S ratio exceeded0.82, MTL was not associated with the high-frequency PTA (**Table 4**).

DISCUSSION

The present nationwide cross-sectional study identified a relationship between telomere length and hearing threshold shifts of adults residing in the United States and indicated that MTL was inversely associated with the high-frequency PTA in a non-linear manner after adjusting for sex, age, race, education level, BMI, noise exposure, hypertension, diabetes, and cigarette smoking (**Figure 2** and **Table 4**). To the best of our knowledge, it is the first cross-sectional study on the relationship between telomere length and hearing threshold shifts of adults in the United States. The findings of this study suggest that telomere length might be a potential predictive biomarker of hearing threshold shifts.

Mammalian telomeres are composed of tandem repeats of the hexanucleotide sequence TTAGGG and several DNA-binding proteins (Blackburn et al., 2015). Telomeres shorten during every cell division with the shortening rate varying among the species, suggesting that they are determinants of species' life spans and have hallmarks of aging (Whittemore et al., 2019; Chakravarti et al., 2021). A large number of studies have been conducted to prove the correlation between MTL and age-related chronic diseases or disorders, such as cardiovascular disease, cognitive performance, and cancer mortality (Huang et al., 2020; Linghui et al., 2020; Shen et al., 2020; Hoffmann et al., 2021). However, studies on the relationship between MTL and hearing loss, which

TABLE 3 | Multivariable linear regression models for outcome of hearing thresholds.

MTL	β (95% CI), *P* value of PTA levels, dB		
	Crude Model	**Model I**	**Model II**
Low-frequency PTA			
MTL (per 1T/S increment)	−5.01 (−6.19, −3.84) < 0.0001	−1.56 (−2.68, −0.43) 0.0067	−1.12 (−2.22, −0.01) 0.0474
Q1	Reference	Reference	Reference
Q2	−0.58 (−1.48, 0.33) 0.2114	0.33 (−0.50, 1.16) 0.4303	0.46 (−0.35, 1.27) 0.2656
Q3	−1.72 (−2.62, −0.82) 0.0002	0.17 (−0.67, 1.01) 0.6936	0.46 (−0.36, 1.28) 0.2695
Q4	−3.28 (−4.17, −2.39) < 0.0001	−0.76 (−1.61, 0.09) 0.0808	−0.42 (−1.25, 0.41) 0.3176
P for trend	< 0.0001	0.0616	0.2938
Speech-frequency PTA			
MTL (per 1T/S increment)	−6.90 (−8.29, −5.51) < 0.0001	−1.76 (−2.98, −0.54) 0.0048	−1.20 (−2.40, 0.00) 0.0503
Q1	Reference	Reference	Reference
Q2	−1.10 (−2.17, −0.03) 0.0445	0.26 (−0.64, 1.17) 0.5666	0.33 (−0.55, 1.21) 0.4629
Q3	−2.87 (−3.94, −1.80) < 0.0001	−0.08 (−1.00, 0.83) 0.8572	0.20 (−0.70, 1.09) 0.6657
Q4	−4.61 (−5.67, −3.55) < 0.0001	−0.83 (−1.76, 0.09) 0.0783	−0.43 (−1.33, 0.47) 0.3501
P for trend	< 0.0001	0.0488	0.2962
High-frequency PTA			
MTL (per 1T/S increment)	−12.99 (−15.66, −10.31) < 0.0001	−2.07 (−4.26, 0.13) 0.0648	−1.09 (−3.27, 1.09) 0.3278
Q1	Reference	Reference	Reference
Q2	−2.89 (−4.95, −0.84) 0.0059	0.00 (−1.62, 1.62) 0.9983	−0.05 (−1.65, 1.55) 0.9494
Q3	−6.55 (−8.59, −4.50) < 0.0001	−0.66 (−2.30, 0.97) 0.4276	−0.46 (−2.08, 1.16) 0.5771
Q4	−8.93 (−10.96, −6.90) < 0.0001	−0.91 (−2.57, 0.74) 0.2806	−0.25 (−1.89, 1.39) 0.7637
P for trend	< 0.0001	0.2008	0.6687

Crude Model = unadjusted. Model I = Crude Model + sex, age. Model II = Model I + race, education level, BMI, noise exposure, hypertension, diabetes, cigarette smoking.
MTL, mean telomere length; CI, confidence interval; PTA, pure tone average.

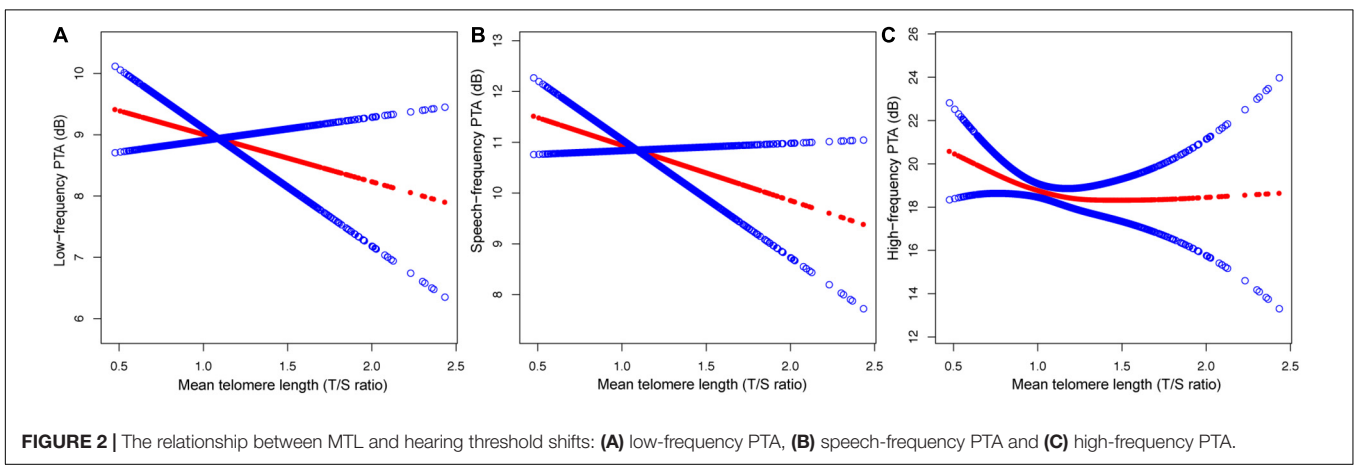

FIGURE 2 | The relationship between MTL and hearing threshold shifts: **(A)** low-frequency PTA, **(B)** speech-frequency PTA and **(C)** high-frequency PTA.

TABLE 4 | The results of two-piecewise linear regression model between MTL and hearing thresholds.

Exposure variables	Low-frequency PTA	Speech-frequency PTA	High-frequency PTA
Cut off point of MTL	1.14	1.06	0.82
< Cut off point of MTL	0.79 (−1.45, 3.02), 0.4913	0.26 (−2.73, 3.25), 0.8661	−21.45 (−37.28, −5.62), 0.0080
≥ Cut off point of MTL	−2.56 (−4.41, −0.72), 0.0065	−1.88 (−3.64, −0.13), 0.0358	0.18 (−2.21, 2.57), 0.8809
Loglikelihood ratio test	0.054	0.294	0.011

is a very common age-related chronic disorder, are quite limited, with results of inverse or negative associations between them (Liu H. et al., 2017; Wang et al., 2019; Zhang et al., 2020). Our results are rather consistent with the results of two previous case-control studies of the Chinese population (Liu X. et al., 2017; Zhang et al., 2020). However, no sex difference was observed

in the role of telomere shortening in hearing loss in our study, which is inconsistent with a previous report (Zhang et al., 2020). Study designs and methods may be one of the reasons for the inconsistent results among different studies. Multiple factors, such as racial heterogeneity and environmental factors, different methods of auditory and MTL measurements, and different sample sizes should be considered (Aubert and Lansdorp, 2008; Ishikawa et al., 2016; Wang et al., 2019).

The MTL was inversely related to high-frequency PTA before a turning point (T/S ratio $= -0.82$). The possible mechanisms are as follows: first, telomere length is inversely associated with aging, and high-frequency PTA increases with age; and second, telomere length is closely related to inflammation, oxidative stress, and inhibition of DNA repair, which play an important role in the development of age-related hearing loss (Rizvi et al., 2014; Zhang et al., 2016). Oxidation damage, including cochlear DNA damage caused by reactive oxygen species (ROS), plays a causal role in the development of hearing loss (Someya et al., 2009). Due to the enrichment of the GGG triplet, telomeres are also highly sensitive to damage by ROS (Houben et al., 2008). Further studies among longitudinal cohorts across different life stages and measurement of MTL in the ear tissue are necessary to confirm these findings. Further experimental studies are needed to explore the mechanisms underlying these findings.

Our study has several strengths. The data in this study were obtained from a large and nationally representative sample from the NHANES, which were standardized and reliable. Participants with abnormal results of the otoscopic examination and poor-quality results in tympanogram or tympanogram compliance of $\leq$0.3 ml were excluded to avoid analyzing data for conductive or mixed hearing loss.

Despite these strengths, the limitations of this study should be considered. The results of this study were not validated because the NHANES is a cross-sectional study. The data representing noise exposure was from a pre-exam audiometric questionnaire involving noise exposure 24 h before the audiometric examination, which may not have reflected the accurate noise exposure status of participants. Some potential confounders were not calculated in the models.

CONCLUSION

According to the results of the NHANES data analyses, MTL was associated with high-frequency PTA hearing threshold shifts of adults in the United States in a non-linear manner. MTL might be a potential predictive biomarker for hearing loss.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Center for Health Statistics Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL made formal analysis of data and wrote the original draft. ZM completed the methodology. ZJ and XT completed the conceptualization, review and editing, revising, and final approval, and are accountable for all aspects. All authors have approved the final manuscript as submitted.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.770159/full#supplementary-material

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Age-Related Decline of Speech Perception

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Hearing loss is one of the most common disorders worldwide. It affects communicative abilities in all age groups. However, it is well known that elderly people suffer more frequently from hearing loss. Two different model approaches were employed: A generalised linear model and a random forest regression model were used to quantify the relationship between pure-tone hearing loss, age, and speech perception. Both models were applied to a large clinical data set of 19,801 ears, covering all degrees of hearing loss. They allow the estimation of age-related decline in speech recognition for different types of audiograms. Our results show that speech scores depend on the specific type of hearing loss and life decade. We found age effects for all degrees of hearing loss. A deterioration in speech recognition of up to 25 percentage points across the whole life span was observed for constant pure-tone thresholds. The largest decrease was 10 percentage points per life decade. This age-related decline in speech recognition cannot be explained by elevated hearing thresholds as measured by pure-tone audiometry.

Keywords: hearing loss, speech perception, age-related hearing loss (ARHL), random forest regression, machine learning, maximum word recognition, speech audiometry

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INTRODUCTION

More than 5% of the world's population, approximately 460 million people, suffer from disabling hearing loss (WHO, 2021). Hearing disability is associated with reduced speech perception and, in consequence, reduced communication function. Hearing deteriorates with age (Zwaardemaker, 1891; Technical Committee ISO/TC 43 Acoustics, 2017). The ISO standard describes the age-dependent frequency-specific loss (ISO 7029:2017, 2017). The slope of the decline increases with growing age and frequency: While for 250 Hz the decline is in the order of 1 dB per decade in the fourth life decade, about 20 dB per decade can be observed for 6,000 Hz in the eighth life decade. While the ISO standard provides detailed information about the relationship between age and pure-tone sensitivity loss (PTSL), it makes no reference to speech recognition.

Given our ageing society and the prevalence of age-related hearing loss (ARHL), it is clear that hearing loss is a common public-health issue of increasing importance in the near future (WHO, 2021). Individuals with ARHL experience social withdrawal (Pronk et al., 2011), mental and physical decline (Shukla et al., 2020), and poorer quality of life (Davis et al., 2007).

Speech perception deficits in hearing-impaired people are mainly attributable to decreased audibility of the speech signal over part or all of the speech frequency range. Within Carhart's (1951) framework for word recognition in quiet, this was referred to as *loss of acuity*. Additionally, Carhart introduced a second component which stems from impaired processing of the audible speech signal, resulting in a *loss of clarity*. Plomp (1978) referred to these components of hearing loss as *attenuation* (class A) and *distortion* (class D), respectively. The attenuation component can be assessed by pure-tone audiometry. The distortion component describes the impact of reduced temporal and frequency resolution. It is thought that the distortion component explains the deterioration of speech recognition which is not described by attenuation, namely pure-tone thresholds. Both attenuation and distortion are part of ARHL (van Rooij et al., 1989).

A large number of studies have focussed upon hearing in the elderly and have investigated PTSL and speech perception. However, the interpretation of these results remains challenging, as pure-tone thresholds change substantially with increasing age. Hence, it is necessary to correct for the effect of PTSL when investigating the effect of age on speech perception. One of the first attempts to do this was described by Jerger (1973) in a report on speech recognition in a large group of older subjects. He analysed scores from the clinical records of 2,162 patients. With subjects grouped according to age and average hearing loss at 0.5, 1 and 2 kHz, results suggested that speech recognition, defined as the maximum score (WRS_{max}) obtained by using a monosyllabic word list, declines above the age of sixty. In particular, he found that age had an effect on speech recognition of approximately 4% per life decade for individuals with mild hearing loss, but that it had a greater effect (e.g., 10% per decade) upon those with higher degrees of hearing loss. Unfortunately, he did not report on hearing loss at higher frequencies. It is known for a long time that hearing thresholds at these higher frequencies are, in particular, worse for older subjects (Zwaardemaker, 1891; Technical Committee ISO/TC 43 Acoustics, 2017).

Several studies have revealed that deterioration in speech understanding occurs in addition to deterioration in hearing sensitivity and includes components beyond elevated hearing thresholds (Bergman et al., 1976; Jerger and Hayes, 1977; Marshall and Bacon, 1981; Pedersen et al., 1991; Divenyi and Haupt, 1997; Kronlachner et al., 2018).

Some authors (Dubno et al., 1997; Humes, 2007) have highlighted the challenge of separating varying auditory thresholds from age, a factor affecting all sensory modalities (Humes and Young, 2016). In recent studies, speech recognition and its relation to age were investigated either by correcting for PTSL (Hoppe et al., 2014; Müller et al., 2016) or by using a longitudinal study design (Dubno et al., 2008). In a clinical population Hoppe et al. (2014) investigated speech recognition with hearing aids and WRS_{max} for different age groups in relation to average hearing loss at 0.5, 1, 2, and 4 kHz (4FPTA). They found a monotonic decrease in speech recognition with increasing age and a significant drop of about 2–4% per decade. This drop was attributed to age-dependent distortion. Müller et al. (2016) investigated, as well, the WRS_{max} as a function of age. After correcting for 4FPTA they found a significant, though smaller, drop for people aged above 70 years of about 2–3% per decade. Neither study included a hearing threshold beyond 4 kHz, and therefore, a small overestimation of the influence of age cannot be excluded. However, Dubno et al. (2008) found a larger effect, around 7–8% per life decade. They performed a longitudinal study including 256 subjects with age-related hearing loss, aged 50–82 years, over a period of 3–15 years. The speech recognition scores were corrected for by changing hearing thresholds during the observation phase; this was done by using the individuals' articulation index as an importance-weighted metric for speech audibility. Unfortunately, longitudinal studies suffer from other disadvantages relating to population size, loss of follow-up etc., and their duration can approach the limits of the clinician's working life span. The special characteristics of the study population and methods—neither the WRS_{max} nor hearing-aid scores were measured—differ from the studies mentioned above. This impedes a direct comparison with the above-mentioned studies and therefore does not imply a contradiction amongst them.

In summary, increased PTSL is the most common expression of ARHL. However, there is evidence that a number of other auditory functions are affected as well (Profant et al., 2019). These functions decline with increasing age and the PTSL does not predict speech recognition sufficiently well.

The goal of this study is to describe the relationship between hearing loss, age, and speech recognition by means of a machine-learning algorithm (Random Forest Regression, RFR, Breiman, 2001). RFR is an algorithm that uses an ensemble method of decision-tree-based regressions to determine a response from a set of input variables. It does not rely on any particular assumptions regarding data distribution. This algorithm is applied to a large data set from routine clinical audiometry in order to investigate the influence of age. The result is a representation of the relationship between pure-tone thresholds and age on the input side and speech recognition on the target side. The model reflects the influence of the age-related distortion component on speech perception.

Additionally, the results of the RFR model will be compared with those of a generalised linear model (GLM) approach. In contrast to the RFR, the GLM requires assumptions about the qualitative relation between input and target variables, whereas the RFR does not need a pre-defined equation framework.

In order to categorise pure-tone thresholds, standard audiograms as proposed by Bisgaard et al. (2010) are used as model input. Both derived models (the RFR and GLM) will be applied to these standard audiograms.

MATERIALS AND METHODS

Audiometric data were retrieved from a clinical data base at the Audiological Department of Erlangen University Hospital. From the routine audiometric measurements, pure-tone thresholds for both bone and air conduction were extracted. Additionally, speech recognition scores for monosyllabic word lists of 20 items for each presentation level of the Freiburg Test (Hahlbrock, 1957)

were evaluated. The complete discrimination function, ranging from 65 dB_{SPL} up to 120 dB_{SPL} was measured. All measurements had been conducted in clinical routine in sound-shielded booths with clinical class A audiometers (AT900 / AT1000 AURITEC Medizindiagnostische Systeme GmbH, Hamburg, Germany). Approval for this study was received from the Institutional Review Board of the University of Erlangen (Ref. No. 162_17 Bc). All methods were carried out in accordance with relevant guidelines and regulations.

Data Preparation

Among 91,991 patients who underwent audiometry at our centre from 2002 to 2020 we identified 53,782 adults aged at least 18 years at the time of first investigation. Initially, the data were screened for repeated measurements. Only the first audiometric assessment of each patient was retained. Subsequently, the data from 107,564 ears (hereinafter "cases") were checked for a complete set of air and bone conduction thresholds. After removal of incomplete data sets there remained 107,010 cases. In the next step, cases with missing or incomplete speech audiometry data were deleted, whereafter 26,324 cases remained. The data were then screened for cases of mixed hearing loss; the latter was defined as a difference between air and bone conduction thresholds greater than 10 dB for frequencies within the range 0.5–3 kHz. After removal of mixed-hearing-loss cases, the remaining 19,929 cases were checked for inconsistent results (<1%) caused e.g., by simulation or lack of collaboration on the part of the patient. If, within the discrimination function for monosyllabic words, a score larger than zero was observed while the presentation level was below the hearing threshold, the data set for that case was not used. For some cases it was observed that the measurement of the discrimination function had not been fully completed, so that a score of 100% was not reached, with the presentation level well (>15 dB) below the discomfort level. Those cases were removed as well. The 19,801 cases (19,801 ears of 12,040 patients) finally remaining were used for model-building and for error analysis.

The following data were used for analysis:

1. Air-conduction hearing thresholds at 0.125, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 kHz,
2. Word recognition score at 65 dB_{SPL} (WRS_{65}),
3. Maximum word recognition score (WRS_{max}) and corresponding level (L_{max}).

WRS_{65} describes speech perception at a typical conversational level. While WRS_{65} is primarily dependent on the attenuation and reflects the loss of speech perception ability in everyday life, WRS_{max} describes the maximum information that can be processed to the auditory system. The difference WRS_{max} – WRS_{65} can be used to estimate the acceptance of acoustic amplification (Halpin and Rauch, 2012).

In order to summarise audiometric constellation of our study population we used an established WHO classification (Olusanya et al., 2019). The average of hearing thresholds, measured at 0.5, 1, 2, and 4 kHz (4FPTA) was used to classify according to the WHO categories: WHO_0 ($\leq$ 25 dB_{HL}), WHO_1 (26 dB_{HL} < 4FPTA $\leq$ 40 dB_{HL}), WHO_2 (40 dB_{HL} < 4FPTA $\leq$ 60 dB_{HL}), WHO_3 (60 dB_{HL} < 4FPTA $\leq$ 80 dB_{HL}) or WHO_4 (80 dB_{HL} < 4FPTA). The Kruskal–Wallis Test was used for group comparisons of the medians for WRS_{65} and WRS_{max}.

Model Setup

For data analysis, model calculation, statistics and figures, the software Matlab *R2019B* including the *Statistics and Machine Learning Toolbox V11.6* (The Mathworks Inc. Natick, Massachusetts) was used. Data were rounded before the RFR model calculation: hearing thresholds to 5 dB and the patients' ages to life decades. Two models (GLM and RFR) were used to describe the relationship between age and PTSL as input variables and speech recognition variables (WRS_{65}, WRS_{max} and L_{max}) as target variables. Equation 1 describes the applied GLM for the target variables WRS_{65} and WRS_{max}. Equation 2 describes the GLM for L_{max}.:

$$WRS\,[\%] = \frac{100}{1 + e^{-\left(\beta_0 + \sum_{i=1}^{i=11}\ \beta_i \cdot PTSL_i + \beta_{12} \cdot Age\right)}} \quad (1)$$

$$L_{max}\left[dB\right] = \beta_0 + \sum_{i=1}^{i=11} \beta_i \cdot PTSL_i + \beta_{12} \cdot Age \quad (2)$$

$PTSL_i$ refer to the air-conduction hearing thresholds at the test frequencies 125 Hz to 8 kHz as mentioned above. In order to represent correctly the overall data distribution according to age and 4FPTA, a stratified fivefold cross-validation was applied. In detail, both models, the RFR and GLM, were trained with 80% of the data (training group). The models were then tested in the remaining 20% of the study population (test group). Before group assignment, the data sets were sorted according to 4FPTA and age. Subsequently, every fifth data set was assigned to the test group. This procedure was repeated five times with disjoint training and test sets. The pure-tone thresholds at all frequencies and the patients' age were input variables, while the WRS_{65}, WRS_{max} and L_{max} were targets. For each of the three output variables a separate model was built.

As a parameter for optimisation and estimating the RFR performance, the median absolute error (MAE, resulting from measured minus predicted score) was used as cost function for both the training group and the test group. The MAE of the test group varied up to 25% for different parameters.

For a large range (50–1,000) of the number of learning cycles (equivalent to number of decision trees) the resulting MAE varied by less than 10%. Finally, a value of 100 for the number of learning cycles was used. A small effect on the MAE was found for the other parameters as well. In summary, the following values were used for the Matlab function "fitrensemble()": "MergeLeaves" = off, the decision tree does not merge leaves. "MinLeafSize" = 5, the minimum number of observations per leaf. "MinParentSize" = 10, the minimum number of observations per branch node. "NumVariablesToSample" = square root of the number of predictors for classification. "PredictorSelection" = allsplits, selects the split predictor that maximises the split-criterion gain over all possible splits of all predictors. The number of nodes per

binary decision tree, one result of the model calculation, varied for each model: around 2,150 for WRS_{max}, around 2,700 for WRS_{65}, and around 3,650 for L_{max}.

The RFR and GLM were applied to Bisgaard standard audiograms. These standard audiograms are well established and widely used for audiological investigations (e.g., Tu et al., 2021; van Beurden et al., 2021). They are based on a large clinical data base. The standard set comprises ten standard audiograms (see **Figure 1**) covering a frequency range of 250 Hz to 6,000 Hz. Flat and moderately sloping (N_1–N_7) and steep (S_1–S_3) audiograms are considered. Higher indices correspond to greater PTSL.

RESULTS

Figures 2, **3** depict the basic characteristics of the clinical population investigated. The stacked bar plot (**Figure 2**) shows the case distribution in our clinical population (N = 19,801). The mean ages of the different groups were 50, 61, 66, 65, and 59 years for WHO_0, WHO_1, WHO_2, WHO_3 and WHO_4. The vast majority (77%) of cases involved persons between 40 and 80 years of age. The subjects aged 40–80 years dominated all WHO grades except WHO_0. The smallest data coverage with respect to age and hearing loss was observed for very young adults in the WHO_4 group and for subjects above 80 years of age in the WHO_0 group.

The speech audiometric results for the model's target scores, WRS_{65} and WRS_{max}, are shown in **Figures 3A,B**, respectively. For both measures the median decreased with increasing degrees of hearing loss. The Kruskal–Wallis Test yielded significant group effects for WRS_{65} ($\chi^2 = 15.055$, $p < 10^{-15}$, df = 4) WRS_{65} and WRS_{max} ($\chi^2 = 11.873$, $p < 10^{-15}$, df = 4). The interquartile ranges for WRS_{65} were 5, 25, 50, 0, and 0% for WHO_0, WHO_1, WHO_2, WHO_3, and WHO_4, respectively. The interquartile ranges for WRS_{max} were 0, 0, 25, 40, and 30% for the corresponding WHO groups. The variability for WRS_{65} was largest for WHO_1, while for WRS_{max} the largest variability was found for WHO_3. In this rather rough classification the interpretation of some outliers may benefit from additional information about the specific configuration of hearing loss. In particular, the WHO classification employs the hearing thresholds at only four frequencies, while other frequencies are not considered. The lowest quartile of the WHO_0 cases shows a WRS_{65} lower than 95%. In this subgroup the mean threshold for high frequencies (>4 kHz) was 48 dB_{HL}, while for the cases with WRS_{65} above 95% in the WHO_0 group the mean threshold for high frequencies was 25 dB_{HL} in the WHO_0 group.

GLM and RFR

Tables 1–3 show the derived GLM parameters β for each target variable including statistical parameters. For the word recognition scores, WRS_{65} and WRS_{max}, the lowest frequency (125 Hz) did not contribute significantly to the model output. None of the other frequencies provided a consistent picture. For L_{max} all but one frequency (750 Hz) contributed significantly to the target variable. For the subject's age the GLM revealed a significant effect on all target variables. For comparison, the permutation feature importance of the RFR is added in the right-hand column of **Tables 1–3**. Larger values for a feature indicate a greater impact on the target variable.

Table 4 summarises the performance of the model as assessed by MAE for both the training and the test group by means of fivefold cross-validation. The results are given separately for the GLM and the RFR model. Owing to the composition of our study population the WHO_0 is by far the largest group. The MAE of this group would have dominated the overall summary. For this reason, **Table 4** shows the error estimation for each grade of hearing loss separately. Evidently, there was a great variation of the MAE among the WHO groups. With the RFR the largest errors were observed in WHO_2 for the WRS_{65} group and in WHO_3 and WHO_4 for WRS_{max}. For those WHO groups the MAE of the training and test groups differed by a factor of 1.5

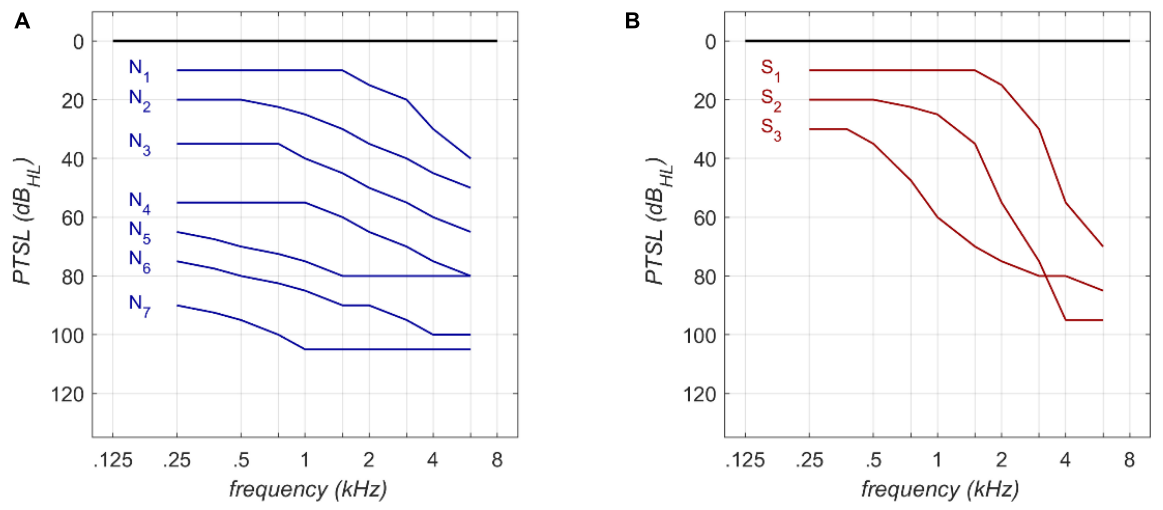

FIGURE 1 | Audiogram types according to Bisgaard et al. (2010) for flat **(A)** and steep **(B)** audiograms.

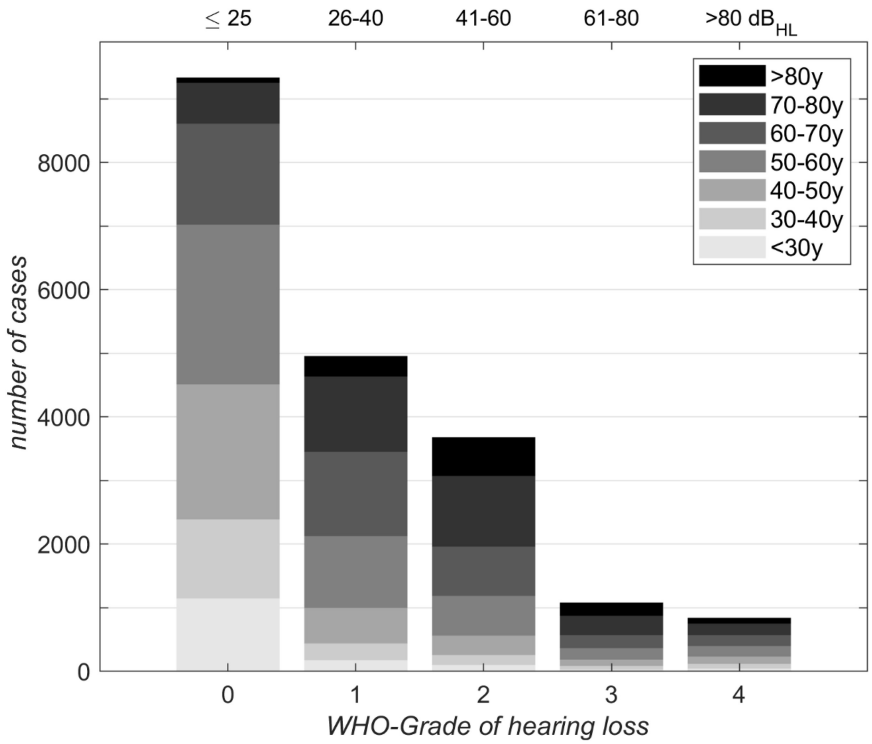

FIGURE 2 | Distribution of 19,801 cases with respect to age for different WHO grades of hearing loss. Corresponding 4FPTA ranges are shown on the upper x-axis.

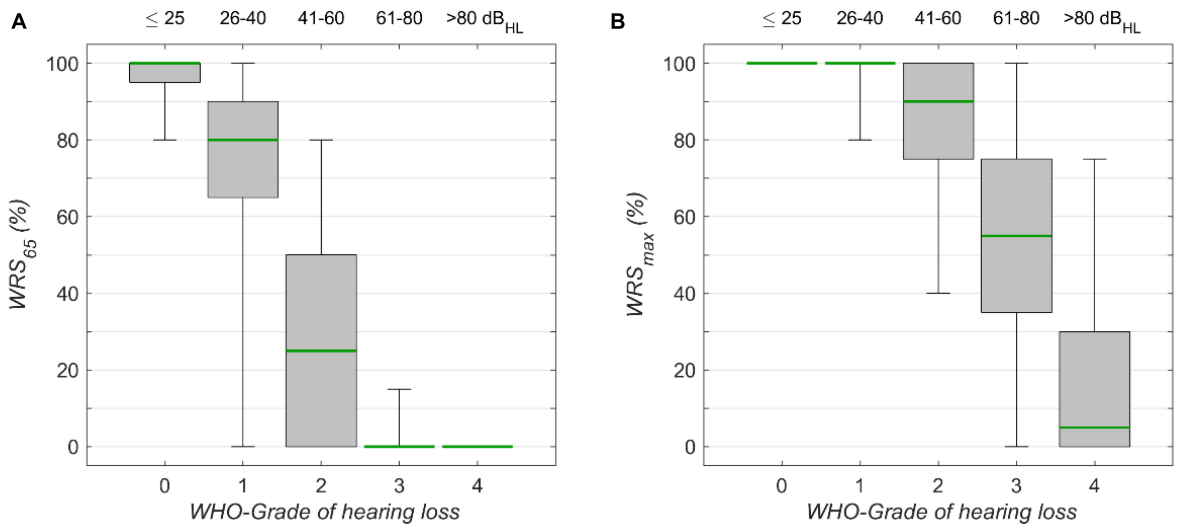

FIGURE 3 | The monosyllabic score **(A)** at 65 dB_{SPL} presentation level (WRS_{65}) and **(B)** the maximum word recognition score (WRS_{max}), for different WHO grades of hearing loss. Corresponding 4FPTA ranges are shown on the upper x-axis. The boxplots show medians (green) with 1st and 3rd quartiles. The whiskers denote the 2.5 and 97.5 percentiles.

to 1.7. Unlike the RFR, the GLM yielded comparable MAE for the training and test groups.

Application of the Model

One possible application of the model is shown in **Figure 4**. The model input was one of the standard audiograms (N_1–N_7, S_1–S_3) and the subjects' age was varied between 18 and 99 years. Owing to the relation between age and hearing thresholds hardly any subjects were in our population aged > 85 years for N_1 and S_1. Therefore, this range was excluded from model calculations.

Figures 4A,D show that both models indicate a decrease in WRS_{65} with increasing age of up to 20 percentage points across

TABLE 1 | GLM parameters for target variable WRS_{65}.

Input variable, corresponding measure	GLM statistics for target WRS_{65}				RFR-WRS_{65} permutation feature importance
	Estimate	Standard error	t-statistic	*p*	
β_0, constant	6.5568	0.0308	212.44	0	n. a.
β_1, $PTSL_{125Hz}$	0.0013	0.0013	0.95	0.34	1.3
β_2, $PTSL_{250Hz}$	−0.0269	0.0018	−15.04	<0.001	1.9
β_3, $PTSL_{500Hz}$	−0.0188	0.0017	−11.20	<0.001	1.9
β_4, $PTSL_{750Hz}$	−0.0071	0.0019	−3.80	0.00015	0.97
β_5, $PTSL_{1000Hz}$	−0.0169	0.0015	10.99	<0.001	2.0
β_6, $PTSL_{1500Hz}$	−0.0190	0.0012	−15.30	<0.001	0.97
β_7, $PTSL_{2000Hz}$	−0.0212	0.0011	−19.02	<0.001	1.5
β_8, $PTSL_{3000Hz}$	−0.0133	0.0010	−13.11	<0.001	1.6
β_9, $PTSL_{4000Hz}$	−0.0100	0.0009	−10.60	<0.001	1.7
β_{10}, $PTSL_{6000Hz}$	−0.0152	0.0008	−20.07	<0.001	2.0
β_{11}, $PTSL_{8000Hz}$	0.0002	0.0005	0.48	0.63	1.3
β_{12}, Age	−0.0122	0.0005	−26.95	<0.001	2.0
	312,280 observations, 312,267 error degrees of freedom χ^2-statistic vs. constant model: 2.10^5, *p*-value < 0.0001				

For comparison the permutation feature importance of the RFR was added in the right column.

TABLE 2 | GLM parameters for target variable WRS_{max}.

Input variable, corresponding measure	GLM statistics for target WRS_{max}				RFR-WRS_{max} permutation feature importance
	Estimate	Standard error	t-statistic	*p*	
β_0, constant	7.1589	0.0425	168.41	0	n. a.
β_1, $PTSL_{125Hz}$	0.0011	0.0007	1.44	0.15	0.76
β_2, $PTSL_{250Hz}$	−0.0047	0.0014	−3.36	0.00079	1.1
β_3, $PTSL_{500Hz}$	−0.0135	0.0019	−7.08	<0.001	1.5
β_4, $PTSL_{750Hz}$	−0.0032	0.0024	−1.30	0.19	1.2
β_5, $PTSL_{1000Hz}$	−0.0136	0.0021	−6.41	<0.001	0.81
β_6, $PTSL_{1500Hz}$	−0.0168	0.0018	−9.13	<0.001	1.2
β_7, $PTSL_{2000Hz}$	−0.0142	0.0017	−8.38	<0.001	0.81
β_8, $PTSL_{3000Hz}$	−0.0081	0.0015	−5.42	<0.001	1.1
β_9, $PTSL_{4000Hz}$	−0.0008	0.0013	−0.63	0.53	1.0
β_{10}, $PTSL_{6000Hz}$	−0.0132	0.0009	−14.22	<0.001	2.1
β_{11}, $PTSL_{8000Hz}$	0.0012	0.0005	2.30	0.022	1.3
β_{12}, Age	−0.0152	0.0005	−27.81	<0.001	1.4
	317,840 observations, 317,827 error degrees of freedom χ^2-statistic vs. constant model: 9.10^4, *p*-value < 0.0001				

For comparison the permutation feature importance of the RFR was added in the right column.

the whole life span. The GLM suggests a rather constant decline of speech recognition over life span. The RFR on the other hand yields specific periods with different amounts of age-dependent decline. The largest decrease was observed for N_3 in the fifth life decade with 10 percentage points per decade.

The RFR results become even more complex if the WRS_{max} and L_{max} are considered, as shown in **Figures 4B,C**, respectively. The presentation level shows, for all types except N_6, an increased presentation level for WRS_{max} with increasing age. A considerable decrease in score can be observed in N_6, accompanied by a slight but significant decrease of L_{max}. For the N_4 and S_3 types the RFR model gives a significant decrease in WRS_{max} which is somehow weakened by an increased presentation L_{max} for this type. For all other types the WRS_{max} does not change with age. However, for these types the RFR model results in an increased presentation level. In comparison, the GLM output indicates a decline for WRS_{max} over age while L_{max} increases for all audiogram types. For both models a decrease of up to 25 percentage points across the whole life span was observed.

DISCUSSION

The analysis of a large clinical database allows the description of the age-related decline of speech perception in detail. In

TABLE 3 | GLM parameters for target variable L_{max}.

Input variable, corresponding measure	GLM statistics for target L_{max}				RFR- L_{max} permutation feature importance
	Estimate	Standard error	t-statistic	*p*	
β_0, constant	48.7010	0.2552	190.81	0	n. a.
β_1, $PTSL_{125Hz}$	−0.0505	0.0093	−5.42	<0.001	1.3
β_2, $PTSL_{250Hz}$	0.0582	0.0160	3.64	0.00028	1.5
β_3, $PTSL_{500Hz}$	0.0908	0.0195	4.66	<0.001	1.4
β_4, $PTSL_{750Hz}$	−0.0016	0.0227	−0.07	0.94	1.4
β_5, $PTSL_{1000Hz}$	0.0437	0.0194	2.25	0.024	0.90
β_6, $PTSL_{1500Hz}$	0.0719	0.0162	4.45	<0.001	1.4
β_7, $PTSL_{2000Hz}$	0.0894	0.0143	6.25	<0.001	1.5
β_8, $PTSL_{3000Hz}$	0.1012	0.0119	8.48	<0.001	2.6
β_9, $PTSL_{4000Hz}$	0.0610	0.0104	5.84	<0.001	2.1
β_{10}, $PTSL_{6000Hz}$	0.0627	0.0088	7.15	<0.001	1.9
β_{11}, $PTSL_{8000Hz}$	0.0407	0.0059	6.92	<0.001	2.4
β_{12}, Age	0.1617	0.0050	32.38	<0.001	2.6
15,892 observations, 15,879 error degrees of freedom F-statistic vs. constant model: 4.10^3, p-value < 0.0001					

For comparison the permutation feature importance of the RFR was added in the right column.

TABLE 4 | Median absolute error and its standard error of the RFR and GLM model for the monosyllabic score at a presentation level of 65 dB_{SPL} (WRS_{65}), the maximum word recognition score (WRS_{max}) and the presentation level for the maximum word recognition score, L_{max}.

Target	Cost function	Subgroup		WHO_0	WHO_1	WHO_2	WHO_3	WHO_4
WRS_{65}	MAE (percentage points)	Training	RFR	1.03 ± 0.04	5.60 ± 0.06	8.01 ± 0.11	0.06 ± 0.02	0.004 ± 0.002
			GLM	1.91 ± 0.01	9.04 ± 0.04	14.36 ± 0.17	2.09 ± 0.04	0.018 ± 0.001
		Test	RFR	1.53 ± 0.08	8.88 ± 0.24	12.70 ± 0.59	0.10 ± 0.05	0.004 ± 0.002
			GLM	1.91 ± 0.01	9.04 ± 0.24	14.42 ± 0.79	2.10 ± 0.11	0.018 ± 0.001
WRS_{max}		Training	RFR	0.04 ± 0.01	1.54 ± 0.02	5.65 ± 0.08	10.79 ± 0.36	6.76 ± 0.27
			GLM	0.57 ± 0.01	3.04 ± 0.03	8.71 ± 0.08	18.92 ± 0.41	8.06 ± 019
		Test	RFR	0.06 ± 0.01	2.27 ± 0.05	9.06 ± 0.25	17.24 ± 1.94	11.28 ± 1.56
			GLM	0.57 ± 0.01	3.04 ± 0.07	8.71 ± 0.26	18.91 ± 1.51	7.82 ± 0.78
L_{max}	MAE (dB)	Training	RFR	3.44 ± 0.04	3.26 ± 0.05	3.39 ± 0.06	3.14 ± 0.13	2.75 ± 0.16
			GLM	5.31 ± 0.04	5.30 ± 0.08	5.85 ± 0.06	5.81 ± 0.11	8.63 ± 0.25
		Test	RFR	5.09 ± 0.17	5.26 ± 0.15	5.41 ± 0.23	5.16 ± 0.46	4.42 ± 0.46
			GLM	5.31 ± 0.18	5.34 ± 0.23	5.85 ± 0.30	5.85 ± 0.55	8.65 ± 1.15

comparison with previous studies, more detailed information about the time course and amount of degradation was achieved by means of RFR. Both models, the GLM and the RFR, describe an age-related decline in speech recognition after being corrected for PTSL. The GLM is based on predefined hypotheses and confirms significant age effects. Inevitably, the relationship between age and speech scores follows the underlying functional relations. The GLM results in an age-related decline for WRS_{max} of about 3–4% per decade for N_4-N_6, and S_3. For all other audiogram types smaller effects were found owing to saturation effects. This is in concordance with previous studies (Jerger, 1973; Dubno et al., 2008). WRS_{65} decreases at a rate of up to 2.5% per decade for mild hearing losses, i.e., $N_{2/3}$ and S_2. For the other audiogram types the GLM yielded smaller rates of decline. Owing to the lower presentation level of 65 dB_{SPL} floor effects were observed even for moderate hearing losses, i.e., N_{4-7}. The RFR model yielded more specific information about the time course and rate of decline. Additionally, the RFR model allows the quantitative description of the two basic effects of hearing loss and its relation to age: On the one hand the impact of the attenuation component of ARHL, and on the other hand the impact of the distortion component of ARHL. This could be achieved by keeping constant the model input variables representing PTSL (attenuation), and by modifying the model input variable representing age. It therefore offers the opportunity to overcome a bias that was immanent in previous investigations (Jerger, 1973; Marshall and Bacon, 1981; Dubno et al., 1997; Hoppe et al., 2014; Müller et al., 2016) by isolating age-related hearing threshold elevation from age-related decline in speech recognition as such.

This study should not be misunderstood as an attempt to predict speech recognition scores on the basis of PTSL. These scores have to be measured individually. The large variability of individual scores necessitates speech audiometry. The purpose of the model in this study was to analyse the impact of age for larger patient populations with respect to specific audiogram

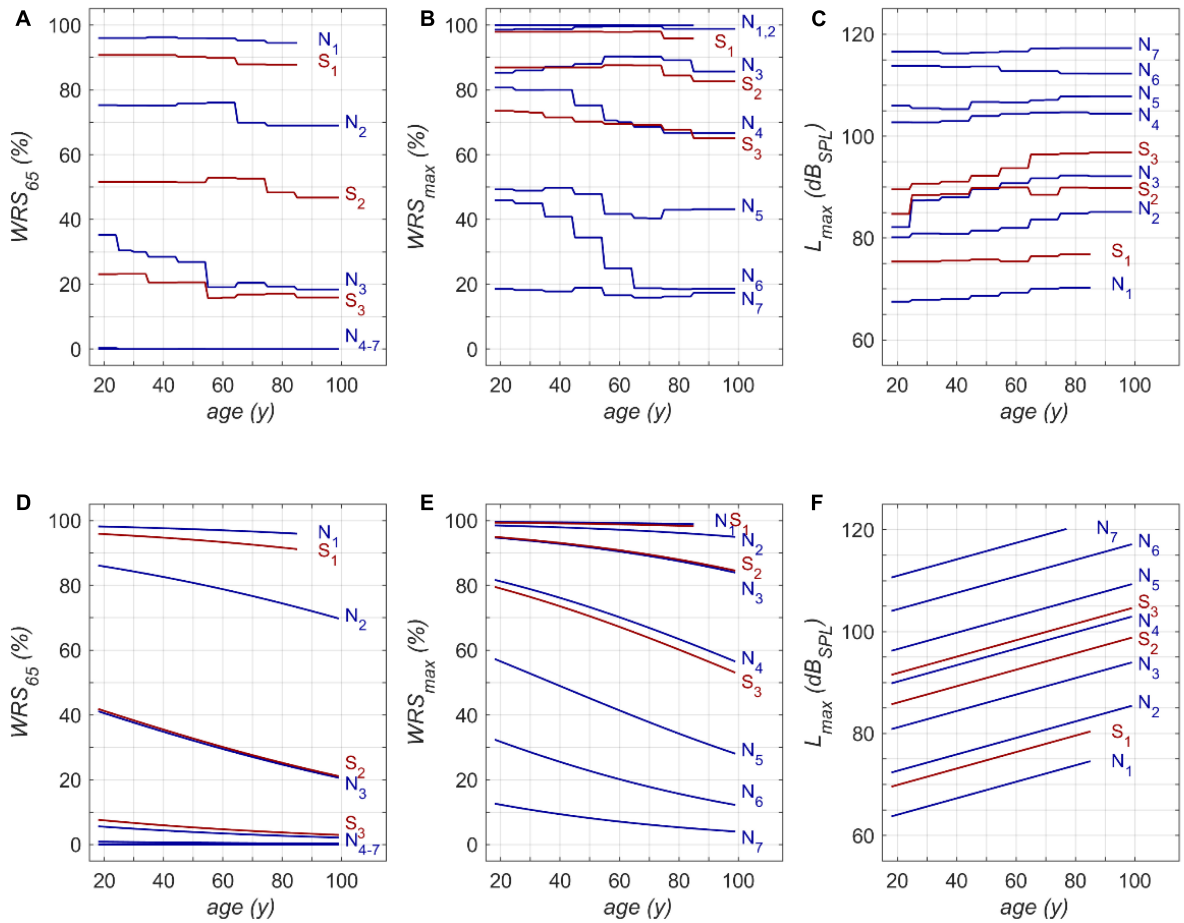

FIGURE 4 | Model results for RFR **(A–C)** and GLM **(D–F)**: **(A)** age dependence of monosyllabic score at 65 dB_{SPL} presentation level (WRS_{65}), **(B)** maximum word recognition score (WRS_{max}) and **(C)** applied presentation level (L_{max}). N_1 to N_7 and S_1 to S_3 refer to the Bisgaard types of audiograms. The second row **(D–F)** shows the results of the GLM equivalent to the upper row **(A–C)**. WRS_{65} and WRS_{max} were calculated according to equation 1 **(D,E)**. L_{max} was calculated according to equation 2 **(F)**.

types. It can be seen in **Figure 4** that those age-related changes are present for the entire duration of adulthood. However, apart from the fact that higher age relates to lower speech recognition scores, no common quantitative trend, for any age groups or PTSL, can be discerned. This may be regarded as the major outcome of the RFR model calculations. The measurable age-related decline in speech recognition depends on the age range considered, the specific audiogram, and the specific application of speech audiometry. Owing to saturation effects of the WRS_{65} measured at typical conversation level, we observed the largest age effect for moderate hearing losses (N_3-type audiograms). For the WRS_{max} measured at substantially higher levels, the largest effects were observed for audiogram types corresponding to severe hearing losses (N_4, N_5, N_6). This result of the RFR is in agreement with findings of Jerger (1973). Even though the variability in his data is considerable (as in our data) one may conclude that a stronger age-related decline can be observed for later life decades and greater hearing loss. Additionally, Jerger's data also indicated that the onset of age-related decline may occur already at younger age. This is in line with our results where the RFR model e.g., yielded for N_6 the strongest decline for WRS_{max} of 20% per decade around the fifth and sixth life decade.

According to the RFR, the decrease in the WRS_{max} was counterbalanced by an increased presentation level for all audiogram types except N_6. The N_6 -type audiogram showed the largest age-related decline in speech recognition. The decreased tolerance of higher presentation levels may have contributed to this decline. This might reflect certain underlying pathomechanisms that are more likely to be present in patients with this audiogram type compared with others. Complementary to attenuation and distortion, a causal and more differentiated breakdown with respect to presbyacusis was proposed early on. Finally, five main types were proposed, namely sensory, neural, metabolic, mechanical, and vascular presbyacusis (Schuknecht, 1964; Johnsson and Hawkins, 1972). This was complemented by the term central presbyacusis in order to reserve the term neural for degeneration of the cochlear nerve. Sensory presbyacusis is congruent with the attenuation component and is, as pointed out above, represented by the audiogram type as a fixed parameter

in **Figure 4**. The effects of all the other types of presbyacusis are included in the specific relationships between age and WRSs, respectively, L_{max}. Moreover, the specific and different root causes may potentially explain why, for some degrees of hearing loss, different changes in speech perception occur in different life decades. However, possible interactions between—or even independent mechanisms—of the main types of presbyacusis are still not completely understood (Bao and Ohlemiller, 2010; Profant et al., 2019).

It is not possible to confirm all these explanatory hypotheses by retrospective data analyses, a fact that clearly underlines the limits of our study design. We found differences in age effects in comparison with some of the studies referred to above. This is partly due to the neglect of hearing loss at higher frequencies for the elderly in those studies. On the other hand, for some hearing losses and audiogram types, this study may underestimate age effects, as ceiling effects of speech tests in quiet are included. Another aspect of this study is the inclusion of a considerable number of subjects with mild hearing loss, as seen in group S_1. Even in that group, age effects play a part. Especially the WRS_{65} illustrates how everyday communicative ability in quiet might be already affected by mild to moderate hearing loss in a population in which the use of hearing aids does not reach the penetration level needed (Halpin and Rauch, 2012).

Other possible applications of the RFR model are related to acoustic amplification with hearing aids: As shown in **Figure 4**, in all groups except N_6, the level for best speech recognition (L_{max}) increases with age at about 0.5 dB per decade. This may indicate that older people may benefit from larger sound pressure levels for speech recognition, i.e., greater amplification, when provided with a hearing aid. As far as we know, current amplification strategies do not take this into account. On the other hand, one has to consider that in some pathologies more amplification might be detrimental rather than beneficial (Halpin and Rauch, 2012).

The age dependence of the WRS_{max} found in our study may be used to improve studies evaluating the outcome of hearing aid use: The WRS_{max} or an equivalent measure is often used as reference for the measurement of successful hearing aid provision or other acoustic amplification (Halpin and Rauch, 2012; Hoppe et al., 2014; Müller A. et al., 2017; Maier et al., 2018a,b), for investigation of age-related changes in cognition (Kronlachner et al., 2018), and for speech-perception-related studies in general (Müller J. et al., 2017). A consideration of both age and specific audiogram type could potentially decrease the variability of results. Furthermore, the functional relation between audiogram types and speech perception as presented here can be used to link epidemiological studies on hearing loss (Sohn and Jörgenshaus, 2001; von Gablenz et al., 2017, 2020; Chang et al., 2019; Löhler et al., 2019; Cantuaria et al., 2021) with speech recognition.

Comparison of the Two Model Approaches

The need for pre-defined hypotheses may be considered a weakness of the GLM, as all model results inevitably follow the underlying analytical equations. If an effect for certain audiogram types is found, the GLM yields a smooth decline over all life decades. The RFR is able to take varying rates of decline in different life decades into account if variation indeed takes place in the study population. Overall, as shown in **Table 4**, for most of the WHO groups the RFR yielded smaller MAE for the test groups compared with the MAE yielded by the GLM. However, the differences obtained between MAE in the training and test groups by RFR indicate some degree of overfitting. This was not the case for the GLM.

The impact of audiometric test frequencies on the calculated WRS is different for the two model approaches. The GLM is less suitable to reflect the impact of low and high frequency hearing loss for all WHO groups. In cases with mild hearing loss higher frequencies have a greater impact: Typically, the low frequencies show low variability and fail to explain the variability in the scores. Vice versa, for cases with severe hearing loss the PTSL for high frequencies are already near or at the audiometer limits. Consequently, the GLM explains the variability in the scores by utilising PTSL in the low–frequency range. As a result for all WHO groups, the GLM suggests that there is no effect of the highest and lowest test frequencies (**Tables 1**, **2**). Some other findings, such as the absence of an effect at 750 Hz on the WRS_{max} in **Table 2**, can be considered as typical signs of an overdetermined system. The measurement at 750 Hz does not provide any additional information compared with the adjacent frequencies and vice versa. *A priori*, there is no audiological rationale for removing single test frequencies.

Limitations of the Study

An important limitation of this study is the restriction to a specific language and test. However, with respect to other languages and speech material the comparison of recent studies (Holden et al., 2013; Hoppe et al., 2019) suggests that the test we used is comparable to the English Consonant-Vowel-Nucleus-Consonant (CNC) test (Causey et al., 1984).

Secondly, the outdated but established calibration procedure for the Freiburg monosyllable test at 65 dB_{SPL} (Holube et al., 2019) is roughly comparable to a level of 60 dB_A. Consequently, L_{max} should be corrected by about 5 dB for a comparison e.g., with CNC results.

The disadvantage of binary decision trees is the high chance of overfitting. The use of a random-forest method decreases this risk. However, a factor of up to 1.7 between the MAEs in the test group as compared with the training group still indicates some degree of overfitting. Even the considerable size of the study population and the clustering of input variables do not entirely prevent this risk. Additionally, there are some intrinsic sources of unexplained variability. Even after thorough data–cleaning as described above, the population may still have included mild cases of aggravation, simulation or dissimulation. There was also a small number of cases with retrocochlear lesions. This number can be estimated as less than 0.5% in our population by comparison with our patient files and the reported incidence (Lin et al., 2005). The unilateral processing of the data without the contralateral status as additional input variable is a potential shortcoming and should be therefore subject to future studies as well.

An RFR model inevitably reflects the characteristics of the clinical population that contributed to the training. The group characteristics differ from those of their peers outside a clinic. Finally, the model reflects the statistical characteristics of a population, and not causal relationships.

CONCLUSION

A random-forest regression model allowed the estimation of age-related decline of speech recognition in quiet, completely separated from the effect of pure-tone sensitivity loss. Noticeable declines were found across the whole duration of adulthood and for all audiogram types. Model calculations resulted in a decrease of up to 25 percentage points word recognition scores across the whole life span. Depending on the specific hearing loss, the RFR model indicated a maximum decline of up to 10 percentage points in certain life decades. The decline can be attributed to an increased distortion component related to presbyacusis which is not represented by pure-tone audiometry. The careful derivation of working hypotheses from our data has the potential to provide greater insight into the relationships between pure-tone sensitivity loss, specific audiogram types and age.

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 human participants were reviewed and approved by Ethik-Kommission, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

UH: conceptualization. UH and TH: formal analysis, writing original draft, methodology, software, validation, and visualization. UH and HI: investigation, project administration, and resources. UH, TH, and HI: writing – review and editing. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Relative and Combined Effects of Noise Exposure and Aging on Auditory Peripheral Neural Deafferentation: A Narrative Review

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Animal studies have shown that noise exposure and aging cause a reduction in the number of synapses between low and medium spontaneous rate auditory nerve fibers and inner hair cells before outer hair cell deterioration. This noise-induced and age-related cochlear synaptopathy (CS) is hypothesized to compromise speech recognition at moderate-to-high suprathreshold levels in humans. This paper evaluates the evidence on the relative and combined effects of noise exposure and aging on CS, in both animals and humans, using histopathological and proxy measures. In animal studies, noise exposure seems to result in a higher proportion of CS (up to 70% synapse loss) compared to aging (up to 48% synapse loss). Following noise exposure, older animals, depending on their species, seem to either exhibit significant or little further synapse loss compared to their younger counterparts. In humans, temporal bone studies suggest a possible age- and noise-related auditory nerve fiber loss. Based on the animal data obtained from different species, we predict that noise exposure may accelerate age-related CS to at least some extent in humans. In animals, noise-induced and age-related CS in separation have been consistently associated with a decreased amplitude of wave 1 of the auditory brainstem response, reduced middle ear muscle reflex strength, and degraded temporal processing as demonstrated by lower amplitudes of the envelope following response. In humans, the individual effects of noise exposure and aging do not seem to translate clearly into deficits in electrophysiological, middle ear muscle reflex, and behavioral measures of CS. Moreover, the evidence on the combined effects of noise exposure and aging on peripheral neural deafferentation in humans using electrophysiological and behavioral measures is even more sparse and inconclusive. Further research is necessary to establish the individual and combined effects of CS in humans using temporal bone, objective, and behavioral measures.

Keywords: cochlear synaptopathy (CS), noise exposure, age-related hearing loss (ARHL), auditory brainstem response (ABR), summating potential to action potential ratio (SP:AP), envelope-following response (EFR), middle ear muscle reflex (MEMR), speech-perception-in-noise (SPiN)

INTRODUCTION

Noise exposure during work and/or leisure activities is associated with a range of disorders including noise-induced hearing loss (NIHL), tinnitus, hyperacusis, temporary threshold shift, compromised sleep, increased stress, and hypertension (Concha-Barrientos et al., 2004; Nelson et al., 2005). The effect of aging on the human auditory system is often described as presbycusis or age-related hearing loss (ARHL); (Huang and Tang, 2010). In ARHL, peripheral and central auditory deterioration takes place which results in a wide variety of auditory symptoms including high-frequency sensorineural hearing loss, impaired sound localization, speech-perception-in-noise (SPiN) difficulties, poor central auditory processing, and impaired temporal processing (Mazelova et al., 2003; Gates and Mills, 2005; Jayakody et al., 2018). Although there is no agreement on a single etiology of ARHL, factors such as genetic predisposition, cumulative lifetime noise exposure, intake of ototoxic medications, and past auditory pathologies may be potential underlying causes (Gates and Mills, 2005; Dubno et al., 2013).

Excessive noise exposure and aging are both associated with major damage to cochlear outer hair cells (OHCs) and their stereocilia, with a lesser impact on inner hair cells (IHCs) (Wang et al., 2002; Gates and Mills, 2005; Popelar et al., 2006; Sergeyenko et al., 2013; Jayakody et al., 2018; Wu et al., 2021). This cochlear hair cell loss often results in a deterioration in hearing sensitivity, loss in frequency selectivity, and worse temporal precision of neural coding (Schuknecht and Gacek, 1993; Ashmore et al., 2010; Salvi et al., 2017). Moreover, atrophy of the cochlear stria vascularis was shown to occur as part of ARHL (Gates and Mills, 2005; Popelar et al., 2006).

In all studied rodent and non-human primate animal species, the synapses between IHCs and afferent auditory nerve fibers (ANFs) degenerate, due to both acoustic over-exposure and aging, before OHCs and IHCs are lost (Kujawa and Liberman, 2015; Valero et al., 2017). This cochlear synaptopathy (CS) has been shown to result in degraded neural temporal processing (Parthasarathy and Kujawa, 2018). Following the loss of cochlear synapses, primary deterioration of afferent ANFs and their spiral ganglion cells (SGCs) occurs (for a review, see Kujawa and Liberman, 2015). Some animal evidence suggests that the majority of lost ANFs are low- to medium spontaneous rate (SR) high-threshold fibers (Schmiedt et al., 1996; Furman et al., 2013), which, in humans, are thought to code moderate-to-high-level sounds, such as speech (Bharadwaj et al., 2014; Kujawa and Liberman, 2015; Huet et al., 2016). However, recent findings by Suthakar and Liberman (2021) have shown that a substantial proportion of high-SR ANFs were lost alongside low-SR ANFs in CBA/CaJ mouse following exposure to intense noise.

The extent to which lifetime noise exposure exacerbates age-related hearing difficulties has been under debate for decades and is generally poorly understood (Shone et al., 1991; Kujawa and Liberman, 2006, 2015; Ciorba et al., 2011). The majority of animal and human research has focused on how each factor separately affects cochlear hair cells and hearing thresholds, with several studies providing evidence that noise exposure may accelerate age-related threshold loss when both factors combine (Shone et al., 1991; Gates and Mills, 2005; Kujawa and Liberman, 2006; Ciorba et al., 2011; Alvarado et al., 2019; Wu et al., 2021; Fetoni et al., 2022).

Recently, consistent research efforts have been made to better understand noise-induced and age-related CS in separation using non-invasive auditory proxy measures. Animal studies have shown a clear relation between noise-induced and age-related synapse loss (occurring in separation) and objective proxy measures such as the amplitude of wave 1 of the auditory brainstem response (ABR) (Kujawa and Liberman, 2009), the middle ear muscle reflex (MEMR) threshold and amplitude (Valero et al., 2016, 2018), the envelope following response (EFR; Shaheen et al., 2015), and the ratio of the summating potential (SP) of the cochlear hair cells to the action potential (AP) of the auditory nerve (SP:AP ratio; Sergeyenko et al., 2013). A large number of human studies have investigated the effects of noise exposure and aging using objective proxy measures of CS, by employing different sample demographics, measurement techniques, and sample sizes. The findings of these studies were generally mixed and inconclusive, making it difficult to draw firm conclusions (Bramhall et al., 2017, 2019, 2021; Prendergast et al., 2017a, 2019; Valderrama et al., 2018; Carcagno and Plack, 2020, 2021; Fernandez et al., 2020).

In this narrative review paper, we will evaluate how noise exposure and aging affect peripheral auditory neural deafferentation independently using: (1) histopathological and neurophysiological; (2) electrophysiological; and (3) behavioral evidence from both animals and humans. For each type of evidence, we will discuss and compare the potential relative and combined effects between these two factors, noise exposure and aging, in relation to CS. All papers included in this review are peer-reviewed published journal articles.

HISTOPATHOLOGICAL AND NEUROPHYSIOLOGICAL ASPECTS

In this section, the histopathological and neurophysiological aspects of noise exposure, aging, and the combined effects of noise exposure and aging, will be discussed in relation to CS in both animals and humans.

Histopathological and Neurophysiological Aspects: Noise Exposure

Animal Studies

Histopathological evidence from several animal species shows that acoustic over-exposure can result in significant CS in basal cochlear regions despite a near-complete recovery of hearing thresholds (Kujawa and Liberman, 2009, 2015; Lin et al., 2011; Furman et al., 2013; Maison et al., 2013; Jensen et al., 2015; Shaheen et al., 2015; Song et al., 2016; Valero et al., 2017; Hickman et al., 2018; Fernandez et al., 2020). Loss of ANFs and SGCs was noted to only be observable several months following the synapse loss in rodents (Kujawa and Liberman, 2015).

Table 1 shows a summary of key studies that investigated the proportion of synapse loss and ABR wave 1 amplitude

TABLE 1 | Summary of key studies on the effect of noise exposure on synapse loss and ABR wave 1 amplitude across different animal species. Data reported were either explicitly mentioned in the manuscript text or were derived from the relevant figures in the respective publications using the online tool of WebPlotDigitizer version 4.5 (Rohatgi, 2021).

Study	Animal species and gender	Age or weight at noise exposure	Noise exposure type, level, and duration	Proportion loss of synaptic ribbons	ABR Stimuli	Maximum ABR wave 1 reduction
Kujawa and Liberman (2009)	Male CBA/CaJ mouse	16 weeks	Octave band of noise (8–16 kHz) at 100 dB SPL, for 2 h	Maximum of 50–60% synapse loss at basal cochlear regions	Tone pips presented at a rate of 30/s (for ABR) or 16/s (for compound action potential) at levels ranging between 10 dB SPL below the threshold to 90 dB SPL in 10-dB ascending steps	72.4% reduction at 32 kHz at 8 weeks following exposure compared to control mice using 90 dB SPL ABR stimuli
Lin et al. (2011)	Female guinea pigs (Hartley strain)	300 g	Octave band of noise (8–16 kHz) at 106- or 109-dB SPL, for 2 h	Maximum of 55% synapse loss at basal cochlear regions	Tone pips at six frequencies ranging from 2 to 32 kHz were presented at a rate of 40/s at levels ranging between 5 dB SPL below the threshold to 80 dB SPL in 5-dB ascending steps	50% reduction at 16 kHz at 2 weeks following exposure (compared to pre-exposure) using 90 dB SPL ABR stimuli
Wang and Ren (2012)	Male and female CBA/CaJ mouse	4 weeks	Octave band noise (12 kHz) at 100 dB SPL, for 2 h, for 3 exposure sessions	Maximum of 65% synapse loss; 40% synapse loss after the first and second exposure sessions. 25% additional synapse loss after the third exposure session	Tone pips or clicks were presented at a rate of 24–32 /s at levels ranging between 70- and 80-dB SPL using 5- or 10-dB ascending steps	70% reduction at 16 kHz in animals with 3 noise exposure sessions using 90 dB SPL ABR stimuli (compared to controls) 60% reduction at 16 kHz in animals with 2 noise exposure sessions using 90 dB SPL ABR stimuli (compared to controls) 40% reduction at 16 kHz in animals with one exposure session using 80 dB SPL ABR stimuli (compared to controls)
Liu et al. (2012)	Male albino guinea pigs	2–3 months (300–350 g)	Broadband noise at 105- or 110-dB SPL, for 2 h	40% synapse loss on average 1-day post-exposure: 15–35% synapse in apical regions and 60–70% synapse loss in basal regions. Synapse recovery was observed 1 month-post exposure with ribbon loss of 10% in high-frequency regions	Clicks were presented at a rate of 11.1/s at 70 dB pe-SPL	53.5% reduction at 8 kHz one month following 110 dB SPL noise exposure compared to controls 40% reduction at 4 kHz cochlear region one month following 110 dB SPL noise exposure compared to controls 24.3% reduction at 16 kHz one month following 105 dB SPL noise exposure compared to controls
Furman et al. (2013)	Female albino guinea pigs (Hartley strain)	1 month (~250 g)	Octave band noise (4–8 kHz) at 106 dB SPL, for 2 h	Maximum of 30% synapse at basal cochlear regions	Log-spaced tone pips with frequencies ranging from 2.8–45.2 Hz at a rate of 30/s and levels ranging from 10–80 dB SPL using 5-dB ascending steps	40% reduction at 16 kHz in noise-exposed animals compared to controls using 80 dB SPL ABR stimuli
Hickox and Liberman (2014)	Male CBA/CaJ mouse	16–18 weeks	Octave band of noise (8–16 kHz) at 94- or 100-dB SPL, for 2 hours	Mice exposed to 100-dB SPL had a maximum synapse loss of 44%, while those exposed to 94 dB SPL showed small non-significant synapse loss compared to controls	Tone pips of frequencies 11.3 Hz and 32 kHz presented at a rate of 40/s at a level ranging from 15–80 dB SPL in 5-dB ascending steps	36% reduction in mice exposed to 100 dB SPL noise (compared to controls) 2 weeks following exposure measured using 32 kHz ABR stimuli at 80 dB SPL 15% reduction in mice exposed to 94 dB SPL noise (compared to controls) 2 weeks following exposure measured using 32 kHz ABR stimuli at 80 dB SPL

(Continued)

TABLE 1 | Continued

Study	Animal species and gender	Age or weight at noise exposure	Noise exposure type, level, and duration	Proportion loss of synaptic ribbons	ABR Stimuli	Maximum ABR wave 1 reduction
Liberman and Liberman (2015)	Male CBA/CaJ mouse	8–9 weeks	Octave band of noise (8–16 kHz) at 98 dB SPL, for 2 hours	Maximum of 55% synapse loss at basal cochlear regions	Tone pips presented at a rate of 30/s at a level ranging from 10 dB below the hearing threshold to 90 dB SPL in 5-dB ascending steps	55% reduction in noise-exposed mice compared to controls at 45 kHz cochlear region. Wave 1 responses were averaged for ABR sound levels of 60–80 dB SPL
Möhrle et al. (2016)	Female Wistar rat	2–3 months	Broadband noise (8–16 kHz) at 100 dB SPL for 2 h	Maximum of 30% synapse loss in the mid-basal cochlear region	Clicks that cover cochlear generators ranging from 2.2 Hz to 13.8 kHz were presented at a level ranging from 20–80 dB above the threshold	35.6% reduction in young noise-exposed rats compared to controls using ABR stimuli of 65 dB above the threshold
Paquette et al. (2016)	Male and female FVB/nJ mouse	60 days post-natal (8.5 weeks)	Octave band of noise (8–16 kHz) at 105 dB SPL, for 0.5 or 1 h	Maximum of 37.5% synapse loss at basal cochlear regions	Tone pips of frequencies 8, 12, 16,24, and 32 kHz or clicks were presented at a level of 15–75 dB SPL	12% and 46% and reduction at 12 kHz 14-days following noise exposure in animals exposed to 0.5 and 1 h of noise respectively (compared to pre-noise) using 75 dB SPL ABR stimuli 69 and 75% reduction at 32 kHz 14 days following noise exposure in animals exposed to 0.5 and 1 h of noise respectively (compared to pre-noise) using 70 dB SPL ABR stimuli
Song et al. (2016)	Male and female albino guinea pig	2–3 months	Broadband noise at 105 dB SPL, for 2 h	45.1% synapse loss averaged across the cochlea at 1-day post-exposure; 17.5% synapse loss averaged across the cochlea at 1-month post-exposure	Not reported	Not reported
Valero et al. (2017)	Male and female rhesus monkey	6.5–11 years	50-Hz noise band centered at 2 kHz at 108-, 120-, 140-, and 146-dB SPL for at least 4-h one exposure session at one level	Monkeys in the temporary threshold shift group showed 12–27% synapse loss averaged across the basal half of the cochlea	Not reported	Not reported
Hickman et al. (2018)	Female chinchillas	6–9 months	Broad-spectrum (0.3–100 kHz) acoustic blast at 160–175 dB SPL, for 1.44 ms	20–45% synapse loss in mid-cochlear and basal regions	Not reported	Not reported
Fernandez et al. (2020)	Male and female CBA/CaJ mouse	16 weeks	Octave band of noise (8–16 kHz) at 97 dB SPL, for 4 h	Maximum of 50% synapse loss in basal cochlear regions	Log-spaced pips of frequencies 5.6–45.2 kHz at a level ranging from below threshold to 90 dB SPL in 5-dB ascending steps	50 and 87% reduction in mice exposed to 97 dB SPL and 100 dB SPL noise respectively 2 weeks following noise exposure at 30 kHz using ABR stimuli of 90 dB SPL

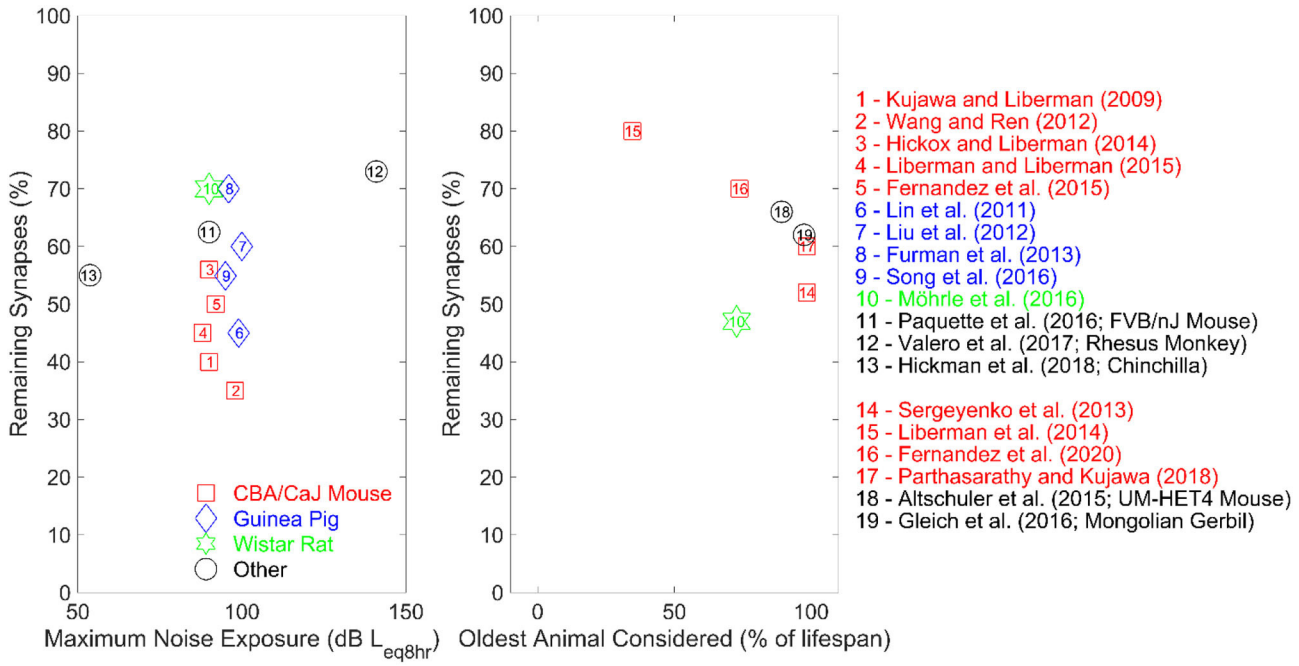

FIGURE 1 | The left panel represents the proportion of remaining synapses as a function of the maximum average noise exposure of the studies summarized in **Table 1**. All studies exposed their subjects to octave-band noise, except for studies numbered 7, 10, and 13 employed broadband noise (study 13 only used blast noise). Studies number 2 and 12 involved multiple noise-exposure session, while all other studies exposed their subjects during one session only. The right panel shows the proportion of remaining synapses as a function of the age of the oldest animals in percent lifespan for the studies summarized in **Table 2**. The reference lifespan for the animals is 25 months for the Wistar rat, 36 months for the Mongolian gerbil and 30 months for both CBA and UMHET4 mouse.

reductions (which is a proxy measure of CS) related to noise exposure across different animal species, for which there were no permanent ABR threshold shifts. Studies suggest that different animal species exhibit variable susceptibility to noise-induced synapse loss. In these studies, the sound pressure level to which animals were exposed was selected such that it was intense enough to produce a temporary threshold shift but not result in permanent threshold elevation.

As shown in **Table 1**, acoustic-over exposure resulted in synapse loss ranging from 12 to 70% primarily in basal regions rather than across the entire cochlea in the absence of threshold elevation in different animal species. Although the majority of the animal literature summarized in **Table 1** employed octave-band noise centered at high frequencies, with few of them using broadband and blast noise insults, the differences in synapse loss could be essentially explained by the fact that the different authors investigated different types of animal species. The left panel of **Figure 1** shows a scatterplot of the proportion of the remaining synapses vs. the maximum noise exposure (standardized as noise intensity in dB of equivalent continuous sound level for 8 h) considered in each study in **Table 1**. The different numbers, shapes, and colors of the data points in the left panel of **Figure 1** reflect the different animal species that were examined in the studies in **Table 1**.

As inferred from the left panel of **Figure 1**, even for very similar noise exposure levels and durations, a wide range of synaptopathic effects were reported across the different animal species. Although animal subjects used were genetically similar in each study (which minimizes inter-subject variability due to genetic makeup), different animal species seem to exhibit different physiologic susceptibility to noise-induced CS. Interestingly, rhesus monkeys, which are physiologically closer to humans than rodents, exhibited the lowest noise-induced synapse loss compared to rodent models, which may be helpful to infer the effect of acoustic over-exposure in humans (Valero et al., 2017). Furthermore, this synapse loss in rhesus monkeys was elicited at much higher intensities than those used in rodent studies (see **Figure 1**), which supports the hypothesis that rhesus monkeys are less susceptible to CS. Dobie and Humes (2017) suggest that humans may be less susceptible to temporary threshold shifts following acoustic overexposure compared to rodents. These findings support the hypothesized variability in auditory system susceptibility to noise damage across different species.

Single-unit recordings suggest that the majority of ANFs lost following CS as a result of acoustic over-exposure in guinea pigs are low- and medium-SR fibers (Furman et al., 2013; Bourien et al., 2014; Song et al., 2016) which are found to represent around 40% of type I ANFs in cats and guinea pigs (Liberman, 1978; Tsuji and Liberman, 1997). In CBA/CaJ mice, significant loss of both low- and high-SR ANFs was seen following intense noise exposure (Suthakar and Liberman, 2021). Low-SR ANFs are observed to have high thresholds in several animal species such as mice, guinea pigs, cats, and gerbils; thus, they are thought to

encode suprathreshold, higher-level, acoustic stimuli (Liberman, 1978; Evans and Palmer, 1980; Huet et al., 2016). However, in rhesus monkeys, Joris et al. (2011) found no evidence that low-SR fibers have higher thresholds than high-SR ANFs. This finding may therefore challenge the assumption that the loss of low-SR ANFs in humans translates into perceptual consequences at higher acoustic stimulus levels, such as SPiN difficulties (Hickox et al., 2017).

Human Studies

In the absence of post-mortum temporal bone data from young noise-exposed humans, it is difficult to precisely predict and quantify the extent to which CS occurs, and the noise levels, types, and duration that may produce CS before hearing thresholds are elevated. However, a recent temporal bone study by Wu et al. (2021) reported that middle-aged human subjects with a documented history of significant occupational noise exposure exhibited an additional 25% ANF loss compared to their low-noise counterparts. Moreover, OHC loss in middle-aged and older human adults with and without occupational noise exposure was highly correlated with ANF loss. Hence, the authors argued that CS may not necessarily be significant and noticeable in humans with minimal OHC loss (i.e., with normal or near-normal hearing thresholds). Instead, the effects of CS may only be clear in individuals with elevated hearing thresholds. Hence, these findings may explain the mixed and inconclusive outcomes produced by CS proxy measures in young normal-hearing humans with a history of acoustic over-exposure as discussed below.

Carney (2018) argues that although low- and medium-SR fibers may not necessarily be involved in the coding of suprathreshold stimuli in humans, their loss may still contribute to deficits in the processing of high-level acoustic stimuli through their involvement in an efferent auditory feedback loop. When this efferent feedback loop is compromised due to either noise exposure or aging, it is thought that it can no longer effectively maintain and enhance signal functional profiles at a wide range of levels and hence would not improve suprathreshold hearing in background noise (Carney, 2018).

Histopathological and Neurophysiological Aspects: Aging

Animal Studies

A progressive loss of cochlear synapses and afferent ANF degeneration is observed in aging rodent models (Sergeyenko et al., 2013; Altschuler et al., 2015; Fernandez et al., 2015; Gleich et al., 2016; Möhrle et al., 2016; Parthasarathy and Kujawa, 2018; Peineau et al., 2021). **Table 2** shows a summary of key animal studies which investigated the proportion of synapse loss and the reduction in the amplitude of wave 1 of the ABR in relation to aging across different rodent species. The right panel of **Figure 1** shows a scatterplot of the proportion of remaining synapses as a function of the age of the oldest age of animals (in percent lifespan) considered in the studies summarized in **Table 2**. The different numbers, shapes, and colors of the data points in the right panel of **Figure 1** reflect the different animal species that were examined in the studies in **Table 2**.

Unlike acute noise-induced CS, which primarily manifests in basal cochlear regions, Fernandez et al. (2015) provided evidence that the cochlear region of noise-induced CS broadens over time to have a widespread impact after a single acoustic trauma. Moreover, age-related synapse loss did not exceed 50% across the different rodent species, whereas acoustic over-exposure seems to account for a higher proportion of synapse loss in some animal studies (Kujawa and Liberman, 2009; Lin et al., 2011; Liu et al., 2012; Singer et al., 2013; Liberman and Liberman, 2015). Furthermore, unlike noise-exposure studies, evidence from aging studies suggests progressive age-related OHC loss that occurs in parallel with synapse loss. A minimal loss of IHCs took place as age progressed and SGC deterioration was slow and uniform across the different cochlear regions (Sergeyenko et al., 2013; Parthasarathy and Kujawa, 2018). Similar to noise-induced CS, the ANFs lost as a result of aging are thought to be predominantly low- to medium-SR fibers (Schmiedt et al., 1996; Kujawa and Liberman, 2015).

Human Studies

Post-mortem human temporal bone studies have confirmed a significant age-related degeneration of SGCs (Otte et al., 1978; Kusunoki et al., 2004; Makary et al., 2011; Nayagam et al., 2011). The percentage of SGC loss seems to be greater in humans with a higher proportion of degenerated cochlear hair cells. For instance, Makary et al. (2011) estimated the rate of SGC loss at around 1,000 per decade in human subjects with normal counts of cochlear hair cells. Otte et al. (1978) reported that this SGC loss rate was doubled (i.e. around 2,000 per decade) in subjects with varying degrees of sensorineural hearing loss compared to subjects with normal cochlear hair cells as shown in the data of Makary et al. (2011). The process of aging seems to affect type I ANFs in humans (Felder and Schrott-fischer, 1995; Chen et al., 2006) such that older adults with high-frequency sensorineural hearing loss were found to exhibit 30–40% type I ANF neuronal degeneration in the absence of significant IHC or SGC loss (Felder and Schrott-fischer, 1995).

More recently, Wu et al. (2019) found that the degeneration of type I ANF peripheral axons due to aging in humans took place well before the loss of OHCs, IHCs, and SGCs. Hence, this is consistent with the primary nature of age-related ANF deafferentation in humans. More than 60% ANF loss (as averaged across the entire standard audiometric range) was estimated to have occurred in human subjects aged over 50 years (Wu et al., 2019). ANF deafferentation was hypothesized to result in the loss of auditory neural information channels, which may render it more difficult for older adults to centrally process speech in the presence of background noise, even when hearing thresholds are within normal limits (as reflected by the normal counts of OHCs) (Wu et al., 2019). However, a caveat to this assumption could be that the relative proportion of low- to medium SR fibers, and their role in higher-level speech perception, are poorly understood in humans.

Wu et al. (2021) determined ANF loss in post-mortum human temporal bones of subjects aged 43–104. The authors estimated

TABLE 2 | Summary of the key studies on the effect of aging on synapse loss and ABR wave 1 amplitude across different animal species. Data reported were either explicitly mentioned in the manuscript text or were derived from the relevant figures in the respective publications using the online tool of WebPlotDigitizer version 4.5 (Rohatgi, 2021).

Study	Animal species/gender	Age of animals	Percentage loss of synaptic ribbons	ABR stimuli	Maximum percentage of the ABR wave 1 reduction
Sergeyenko et al. (2013)	Male CBA/CaJ mouse	4–144 weeks	Maximum of 48% synapse loss at 144 weeks compared to 4 weeks. Age-related synapse loss was fairly uniform across all cochlear regions Maximum of 40% synapse loss at 128 weeks compared to 4 weeks. Age-related synapse loss was fairly uniform across all cochlear regions	Log-spaced tone bursts with frequencies 5.6–45.2 kHz presented at a level ranging from below 5 dB below the threshold to 90 dB SPL in 5-dB ascending steps	95% reduction in 128-week mice compared to 4-week mice at 12 kHz measured using 80 dB SPL ABR stimuli 80% reduction in 96-week mice compared to 4-week mice at 12 kHz measured using 80 dB SPL ABR stimuli 71.5% reduction in 80-week mice compared to 4-week mice at 12 kHz measured using 80 dB SPL ABR stimuli
Liberman et al. (2014)	Male CBA/CaJ mouse	6–45 weeks	Synapse loss in age controls at 45 weeks ranged between 2–20% depending on cochlear location. The proportion of synapse loss in apical and basal areas seems similar (about 10–20%)	Tone busts presented at a rate of 35/s and with a level ranging from 5 dB below the threshold to 80 dB SPL ascending in 5-dB steps	35% in 45-week age-only control mice compared to 8-week control subjects at 17 kHz. Responses were averaged for ABR stimuli ranging between 60–80 dB SPL
Altschuler et al. (2015)	Female UM-HET4 mouse	Three groups: 5–7, 22–24, and 27–29 months	The two older groups exhibited 20–34% synapse loss compared to the young group averaged across cochlear regions examined (i.e., 1–4 mm from the apex). Synapse reduction was significantly less in the 22–24-month group compared to the 5–7-month group. No further significant synapse loss was noted in the 27–29-month group compared to the 22–24-month group in all synapse regions studied	Not reported	Not reported
Fernandez et al. (2015)	Male CBA/CaJ mouse	16–104 weeks	Up to 30% synapse loss in 22.6 kHz cochlear region in age-only controls 96 weeks following noise exposure compared to young controls at 4 weeks following noise exposure. The proportion of age-related synapse loss ranged between 15–30% across different cochlear regions in older age-only controls at 96-weeks following noise exposure	Log-spaced tone bursts of frequencies ranging between 5.6–45.2 kHz were presented at a rate of 30/s at a level from 30–90 dB SPL ascending in 5-dB step increments	66% in 88 weeks following noise exposure (at the age of 104 weeks) in age-only older controls compared to 2 weeks following noise exposure (at the age of 18 weeks) in young controls at 32 kHz using 90 dB SPL ABR stimuli
Gleich et al. (2016)	Mongolian gerbil	Two groups: about 10 and about 38 months	The older group exhibited 21% synapse loss on average (across the entire cochlea) and a maximum of 38% loss at apical cochlear regions compared to the younger group	Not reported	Not reported
Möhrle et al. (2016)	Female Wistar rat	Three pre-noise exposure groups: 2–3, 6–10, and 19–22 months.	The pre-noise exposure groups aged 19–22 months and 6–10 months exhibited 53 and 29% synapse loss respectively in mid-basal cochlear regions compared to the 2–3-month group (pre-noise exposure)	Clicks that cover cochlear generators ranging from 2.2 Hz to 13.8 kHz were presented at a level ranging from 20–80 dB above the threshold	The pre-noise exposure groups of 19–22-months and 6–10-months both exhibited a reduction in the ABR wave 1 amplitude of 40 and 35.6% respectively compared to the 2–3-month pre-noise exposure group at 75 dB above threshold ABR stimuli
Parthasarathy and Kujawa (2018)	Male and female CBA/CaJ mouse	16–128 weeks	Maximum of 40% synapse loss by 128 weeks. A fairly similar age-related pattern of synapse loss in mid-basal and basal cochlear regions	Log-spaced tone bursts ranging from 5.6–45.2 kHz were presented at a rate of 33/s at levels ranging from 10–90 dB SPL	84, 71.1, 50, and 23.4% in 128, 108, 64, and 32-weeks mice respectively compared to 16-week mice at 32 kHz using 90 dB SPL ABR stimuli 84.5, 69, 39.4, and 29.9% in 128, 108, 64, and 32-weeks mice respectively compared to 16-week mice at 12 kHz using 90 dB SPL ABR stimuli

age-related ANF loss at 6.3% per decade. This was noted to take place across the entire human cochlea with more pronounced effects in basal cochlear regions. However, unlike the data reported by Wu et al. (2019), Wu et al. (2021) showed a strong positive correlation between OHC and ANF loss. According to the authors, this positive correlation between OHC and ANF loss contradicts the hypothesized primary nature of ANF loss in humans and hence adds more uncertainty to how age-related CS manifests perceptually in humans with normal/near-normal audiometric profiles. This is because most ANFs that are affected by CS are thought to make contact with IHCs and histopathological animal studies have demonstrated that the loss of CS and afferent ANFs occurs well before OHCs are lost (as discussed earlier). More temporal bone evidence is therefore necessary to establish the relation between ANF and OHC loss over the entire human lifespan.

Viana et al. (2015) counted synaptic ribbons connected with IHCs in older humans and reported that aged ears had no more than 2.0 synapses per IHC at basal cochlear regions (i.e., at about 2 kHz) compared to 11.3–13.3 synapses per IHC in young controls. This translates to approximately 85% age-related basal synapse loss in humans. At more apical cochlear regions (e.g., 0.25 kHz), synapses per IHC did not exceed 7.6 in older ears (i.e., about 40% synapse loss), which suggests that age-related synapse loss in humans may have a bigger impact at basal rather than apical cochlear regions. Synapse loss was reported to take place well before cochlear hair cells were lost. This is thus consistent with Wu et al. (2019) findings concerning the primary nature of peripheral neural deafferntiation. Bharadwaj et al. (2014) predicted that age-related synapse loss most likely occurs at a minimum of 30% in aged humans. This prediction was inferred from mouse data which showed that SGC degeneration occurred 1–2 years following synapse loss. Moreover, this prediction is consistent with the findings of Viana et al. (2015) and with rodent studies summarized in **Table 2** which documented age-related synapse loss of up to 50%. Hence, significant synapse loss may well occur over a human's lifespan given the existing evidence from temporal bones on age-related ANF and SGC degeneration in older humans.

Histopathological and Neurophysiological Aspects: Combined Effects of Noise Exposure and Aging

Animal Studies

In a few animal models, the combined impact of aging and noise exposure on synapse loss has been investigated. Fernandez et al. (2015) determined the pattern of auditory neural degeneration following acute noise exposure across the lifespan of CBA/CaJ mice. Synapse loss was estimated at a maximum of about 55% in older animals aged 96 weeks following exposure to 100 dB SPL noise for 2 h at the age of 16 weeks compared to up to 30% in non-exposed older counterparts. Synapse loss was most significant in basal cochlear regions in both young and older mice. As noise-exposed mice aged further, synapse counts in more apical cochlear regions were found to deteriorate as well. The authors noted, however, that cochlear regions with the most significant noise-induced synapse loss exhibited less synapse degeneration per year (throughout the 96 weeks following the noise exposure) compared to cochlear areas with the lowest noise-induced CS. The authors proposed that this decrease in synapse loss is consistent with the assumption that only a proportion of afferent auditory ANFs may be vulnerable to both noise exposure and aging (Schmiedt et al., 1996; Furman et al., 2013).

Möhrle et al. (2016) reported that young rats exposed to 100 dB SPL noise for 2 h exhibited about 30% synaptic loss in mid-basal cochlear regions compared to controls. The synapse populations following the same noise exposure event in middle-aged and old rats were not significantly different from controls in each age group. Moreover, synaptic counts in middle-aged noise-exposed rats were similar to young noise-exposed animals. Old noise-exposed rats had about 15% fewer mid-basal IHC-ANF synapses compared to their young noise-exposed counterparts.

Human Studies

By assuming either a regular constant acoustic over-exposure throughout the lifespan or exposure to one single event of intense noise, we propose two simple models for the combined effects of noise exposure and aging on CS in basal cochlear regions as shown in **Figure 2**. In this figure, the proportion of remaining synapses is expressed as a function of age ranging from 0 to 100 years. **Figures 2A,B** represent the effects of age and the combined effects of age and constant acoustic overexposure on the proportion of synapse loss, while **Figures 2C,D** illustrate the effects of age and the combined effects of age and a single event of intense noise exposure. For both instances of noise exposure scenarios, we assume that either all IHC-ANF synapses (**Figures 2A,C**) or only low- and medium-SR ANFs (**Figures 2B,D**), which are thought to comprise 40% of type I ANFs in cats and guinea pigs (Liberman, 1978; Tsuji and Liberman, 1997), are vulnerable. It is assumed in the models that age causes the loss of a constant proportion of the remaining vulnerable synapses per unit of time. Similarly, noise exposure is assumed to cause a constant proportional loss of the remaining vulnerable synapses (for a given exposure). In other words, for a given vulnerable synapse, there is assumed to be a constant risk of loss for a given unit of time, or a given exposure. This is why the plots are asymptotic curves, rather than straight lines.

For both noise exposure scenarios of our models, we predict that, although human temporal bone studies have shown that age-related ANF loss may occur at a proportion of more than 60% (Wu et al., 2019), IHC-ANF synapse loss secondary to aging may take place at a more conservative proportion (i.e., 30% in basal cochlear regions) as suggested by Bharadwaj et al. (2014). It is important to acknowledge that the main limitation in temporal bone studies, which may reduce confidence in their findings, is that many human subjects were in poor health prior to death. This may result in over-estimating the effects of aging (since there may be factors other than age contributing to CS and the influence of these factors may increase with age). Moreover, these studies lack precise estimation of noise and ototoxic exposure. Individuals who were not identified as having an occupational noise history could still have had significant lifetime exposure to noise and/or ototoxins. Finally, this difference in ratios may be

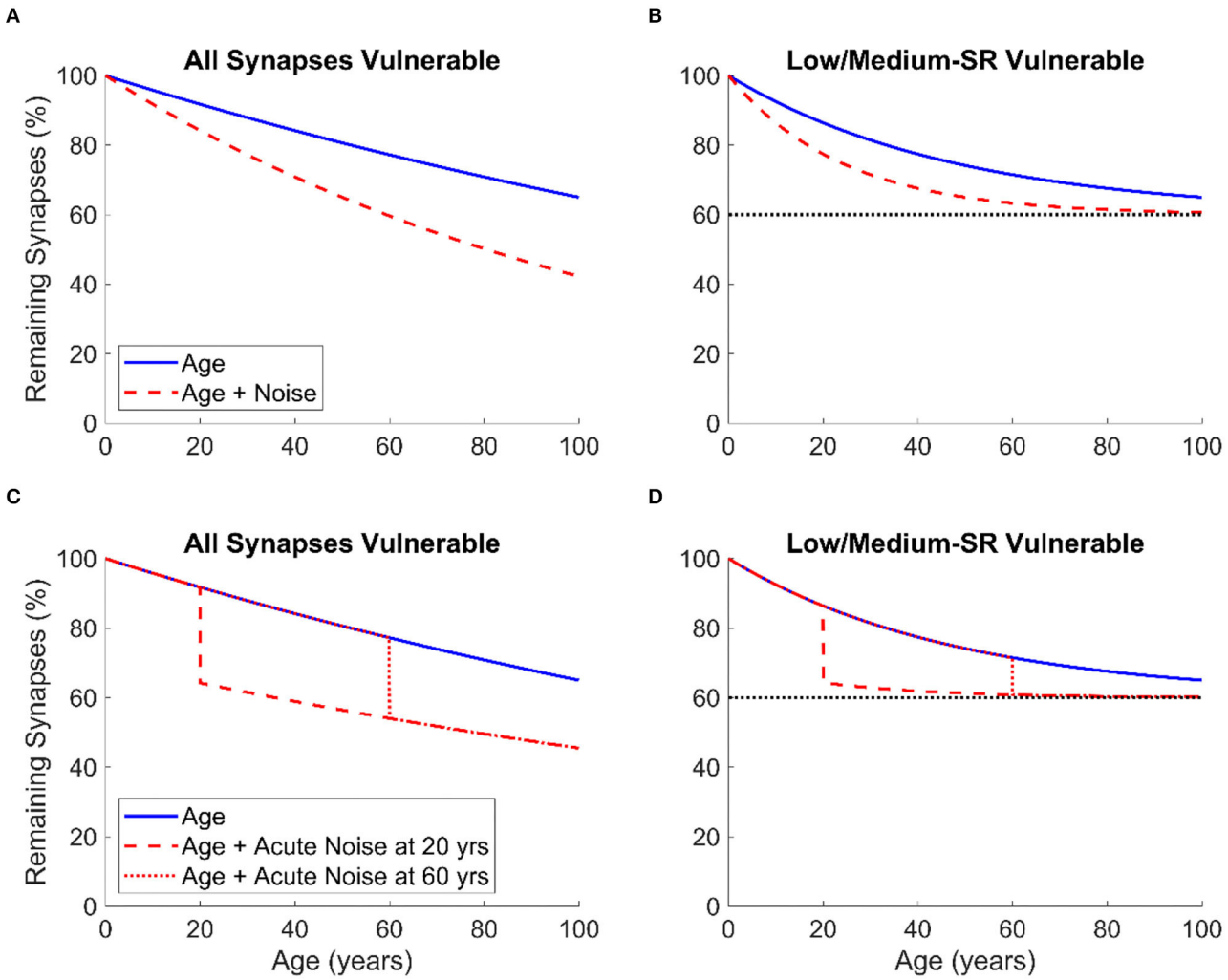

FIGURE 2 | The proportion of remaining IHC-ANF synapses at basal cochlear regions as a function of age in humans given two models of synapse/ANF vulnerability: All synapses vulnerable **(A,C)** and only low- and medium-SR ANFs vulnerable **(B,D)**. The two models are based on two assumptions: regular constant lifetime acoustic over-exposure **(A,B)** and one single event of intense noise exposure occurring at age 20 or 60 **(C,D)**. In **(B,D)**, the dashed line is an asymptotic line defining the percentage of synapse loss beyond which no further CS occurs.

explained by factors other than synapse loss that may account for ANF degeneration such as age-related genetic susceptibility to ANF degeneration.

We also assume that about 30% further synapse loss occurs due to acoustic over-exposure for both noise exposure scenarios. This estimation is based on Valero et al. (2017) data which has shown that 12–27% synapse loss occurred in the non-human primates of macaque monkeys following one intense event of noise exposure. Unfortunately, no animal or human data are available on the proportion of synapse loss secondary to cumulative regular constant lifetime noise exposure. So, we arbitrarily extended the assumption of 30% synapse loss to the scenario of regular acoustic-over exposure across the entire human lifespan.

For the assumption in which all synapses are vulnerable and for both scenarios of noise exposure (**Figures 2A,C**), CS due to noise exposure has a greater overall effect as more synapses are vulnerable. In contrast, synapse loss, either due to aging only or to noise exposure and aging together, saturates to a maximum of 40% if only low- and medium-SR ANFs are vulnerable (assuming that humans have the same proportion of low- and medium-SR ANFs to cats and guinea pigs as discussed above) as shown in **Figures 2B,D**.

It is worth pointing out that this model (as proposed in **Figure 2**) is very simplistic and is intended to be primarily a schematic illustration of the patterns of synapse loss that may occur in human ears secondary to noise exposure throughout the lifespan. However, the model may be useful for relating the expected consequences of different combinations of noise

exposure and aging to objective and behavioral proxy measures in animals and humans.

Recently, the combined impact of both occupational noise exposure and aging in post-mortum human temporal bones was assessed by Wu et al. (2021). Lifetime occupational noise exposure was found to uniformly exacerbate age-related ANF loss across the different cochlear regions in the middle-aged group (i.e., subjects aged 50–74) by 25%, but not in the older group (i.e., subjects aged 75–104). These results are broadly consistent with the assumption we made above that when only low- and medium SR ANFs are vulnerable to both noise exposure and aging, little further CS occurs at older ages once a specific proportion of IHC-ANF synapses has been lost (**Figures 2B,D**). It is important to point out, however, that for the highest cochlear frequency regions considered by Wu et al. (2021) almost all ANFs were lost where a near-complete degeneration of IHCs had occurred. Therefore, the primary cause of this high-frequency ANF loss may not necessarily be CS, but rather IHC loss. This is because the loss of an IHC will lead to degeneration of the associated ANFs, irrespective of the degree of CS.

Wu et al. (2021) reported that IHC loss due to occupational noise exposure was minimal. In contrast, a high correlation between ANF and OHC loss in both basal and apical cochlear regions across different subjects of varying ages and with and without documented occupational noise exposure was found. Hence, the authors suggest that the effects of CS may only be substantial in the presence of threshold elevation in humans. Furthermore, OHC loss, rather than IHC or ANF loss, was found to be the main predictor of subjects' word recognition in quiet.

Given the lack of human temporal bone studies on the effect of noise exposure in isolation, it is difficult to estimate precisely how a history of acoustic over-exposure may impact the populations of cochlear synapses and ANFs at an older age. Given the difficulty in planning and conducting temporal bone studies, it is likely some time before data are available on how noise exposure and aging interact. This lack of studies may stem in part from the fact that it is difficult to retrospectively quantify the extent of lifetime noise exposure in deceased humans. Moreover, such studies may not be successful in controlling for genetic factors and past exposure to ototoxic substances, which may influence the onset and progression of age-related cochlear degeneration as well as the vulnerability to noise exposure at both young and older ages (Pyykkö et al., 2007).

OBJECTIVE PROXY MEASURES OF COCHLEAR SYNAPTOPATHY

In this section, animal and human studies in relation to noise exposure, aging, and the combined effects of noise exposure and aging, will be discussed in the framework of the objective proxy measures of CS: ABR wave I, ABR wave I:V amplitude ratio, SP:AP ratio, EFR, and MEMR.

Auditory Brainstem Response Wave I

Auditory Brainstem Response Wave I: Noise Exposure

Animal Studies

Across different animal species, noise-induced CS, primarily in the absence of hair cell loss, is associated with a 12–72.4% decrease in the amplitude of wave 1 of the ABR to moderate-high level stimuli, as summarized in **Table 1**. In addition to the fact that these studies involved different animal species (which likely exhibit different susceptibility to noise-induced CS), different studies used an exposure of different levels, durations, and spectra of noise. Moreover, the effect of noise exposure was investigated using different ABR stimuli, and measures were made at different frequencies (which may be affected by CS to differing extents). These methodological differences, highlighted in **Table 1**, could at least partially explain the high variability in the percentage of the ABR wave 1 reduction found across the different animal studies. Finally, since the majority of the animal literature summarized in **Table 1** employed animals of single-sex, it is difficult to draw firm conclusions on whether the amplitude of ABR wave 1 varies, and to what extent, as a function of sex.

Human Studies

The effect of excessive noise exposure on the amplitude of wave I of young normal-hearing human adults has been inconclusive. Some studies have reported that a smaller amplitude of wave I of the ABR is associated with high noise exposure in young subjects (Stamper and Johnson, 2015a,b; Liberman et al., 2016; Bramhall et al., 2017, 2021; Valderrama et al., 2018; Buran et al., 2022), while several other studies failed to document such an effect (Grinn et al., 2017; Grose et al., 2017; Prendergast et al., 2017a, 2018; Skoe and Tufts, 2018; Couth et al., 2020). **Table 3** shows a summary of studies that investigated the effect of noise exposure on ABR wave I amplitude in humans. It is worth highlighting that Bramhall et al. (2017, 2021) investigated firearm exposure among military veterans, which is primarily an impulsive type of noise and may hence be different in effect from the recreational exposures considered by the majority of the other human literature (for reviews, see Bramhall et al., 2019; Le Prell, 2019). As highlighted in **Table 3**, the amplitude of ABR wave I of female participants was larger than that of males (Stamper and Johnson, 2015a,b; Bramhall et al., 2017; Grose et al., 2017; Prendergast et al., 2017a; Valderrama et al., 2018). ABR wave amplitudes seem to be influenced by the sex of participants due to the potential variability in lifetime noise exposure (i.e., males may exhibit higher noise exposure than females; Stamper and Johnson, 2015b), and anatomical differences between sexes (such as differences in cochlear dispersion, head size, and bone density; Mitchell et al., 1989; Don et al., 1993). The influence of sex on ABR wave I was not quantified and controlled in all human CS studies. Future studies on CS in humans could be more explicit in considering this factor.

Auditory Brainstem Response Wave I: Aging

Animal Studies

Rodent studies suggest that age-related CS, in the absence of significant lifetime noise exposure, results in reduced amplitude

TABLE 3 | Summary of the methods and findings of the studies that investigated the effect of noise exposure on the amplitude of wave I of the ABR in humans. Data reported were either explicitly mentioned in the manuscript text or were derived from the relevant figures in the respective publications using the online tool of WebPlotDigitizer version 4.5 (Rohatgi, 2021).

Study	Participants	ABR recording parameters	Outcomes	Sex-specific findings
Stamper and Johnson (2015a,b)	30 subjects (20 females). Age 18–29 years. All had normal hearing (hearing thresholds <20 dB HL at 0.25–8 kHz). Participants had various amounts of self-reported lifetime noise exposure. Participants with high lifetime noise exposure were recruited from University music departments	Mastoid and tympanic membrane electrode montages. Click and tone burst at 4 kHz were used at the level of 90 dB nHL and subsequently lowered by 10 dB steps	In Stamper and Johnson (2015a), the ABR wave I amplitude was 42.7% ($p = 0.015$) and 35.4% ($p = 0.095$) smaller on average in high noise subjects compared to low noise counterparts measured using clicks at 90 dB nHL with mastoid and tympanic membrane electrode montages respectively. Measurements using tone bursts of 4 kHz at 90 dB nHL showed the ABR wave I amplitude reduction at 48% ($p = 0.013$) and 43.3% ($p = 0.056$) on average in high noise subjects using mastoid and tympanic membrane electrode montages respectively.	Sex was a confound, with males having the highest noise exposures and the lowest wave I amplitudes Stamper and Johnson (2015a) In a reanalysis, Stamper and Johnson (2015b) reported that the ABR wave I amplitude reductions measured using clicks at 90 dB nHL were only statistically significant (in females ($p = 0.005$), not males ($p = 0.302$; i.e., 43.3% lower wave I amplitudes in high noise females compared to low noise females)
Liberman et al. (2016)	34 young adults (15 females) aged 18–41 were recruited from local colleges and universities in the USA. Participants were allocated into high-risk ($n = 22$) and low-risk ($n = 12$) for ear damage based on self-reported noise exposure	94.5 dB nHL clicks at a rate of 9.1 Hz or 40.1 Hz. In order to eliminate the contribution of the contralateral ear, ipsilateral clicks were presented with a contralateral broadband masker at 55 dB nHL. Ipsi- and contra-lateral tiptroad ear canal montage was used	The high-risk group had a 14.7% smaller ABR wave I amplitude compared to the low-risk group ($p < 0.001$).	The authors repeated the analyses across both sexes of participants separately in order to evaluate any sex effect. The differences originally found remained highly significant in both sex groups after the analyses were run on male- and female-only groups
Bramhall et al. (2017)	100 military veterans and nonveterans aged between 19–35 years. Participants were divided into four groups based on self-reported noise exposure: non-veterans, non-veteran firearm, veteran high noise, and veteran low noise. All participants had normal hearing thresholds	Tone bursts at 1, 3, 4, and 6 kHz at levels ranging between 60 and 110 dB p-peSPL using extra-tympanic electrodes	Measurements obtained at 110 dB p-peSPL: - Using a 1 kHz tone burst ABR wave I amplitude was 33.3% smaller in non-veteran firearm compared to non-veterans and 53.3% smaller in veteran high noise compared to veteran low noise. - Using a 3 kHz tone burst, the ABR wave I amplitude was 22.6 and 33.3% smaller in non-veteran firearm compared to non-veterans and in veteran high noise compared to veteran low noise respectively - Using a 4 kHz tone burst, the ABR wave I amplitude was 20.5 and 26.2% smaller in non-veteran firearm compared to non-veterans and in veteran high noise compared to veteran low noise respectively - Using a 6 kHz tone burst, the ABR wave I amplitude was 15.6 and 16.7% smaller in non-veteran firearm compared to non-veterans and in veteran high noise compared to veteran low noise respectively	A weak sex effect was seen such that females had greater wave I amplitude than males in the veteran high-noise group and the non-veteran group. The ABR wave I sex differences were smaller than the mean ABR wave I differences (across both sexes) between the veteran high-noise and non-veteran groups. Males had slightly smaller wave I amplitudes than females in veteran high-noise and non-veteran groups using different tone burst intensities at 4 kHz

(Continued)

TABLE 3 | Continued

Study	Participants	ABR recording parameters	Outcomes	Sex-specific findings
Grinn et al. (2017)	32 participants (19 females) aged between 21–27 years with normal hearing as defined by hearing thresholds of ≤ 25 dB HL at 0.25–8 kHz	Clicks and tone bursts at 2, 3, and 4 kHz were presented at a level of 70 dB HL, 80 dB HL, and 90 dB HL at a rate of 11.7/s. In-the-canal tiptrode electrode configuration was used with non-inverting and ground electrodes stacked with spacing at midline high forehead (Fz)	After controlling for sex, noise exposure did not predict ABR wave I amplitudes using clicks (p = 0.25; for males r = 0.0736, p = 0.82; for females r = −0.0754, p = 0.759) and tone bursts at 2 kHz (p = 0.88; for males r = −0.114, p = 0.724; for females r = −0.0791, p = 0.747), 3 kHz (p = 0.71; for males r = 0.0346, p = 0.915; for females r = −0.0634, p = 0.803), and 4 kHz (p = 0.22, for males r = −0.008, p = 0.98; for females r = −0.129, p = 0.598) at 90 dB nHL	Females had significantly larger wave I amplitudes than males at 90 dB HL (for clicks p = 0.002; for 2 kHz p = 0.006; for 3 kHz p = 0.004; for 4 kHz $p < 0.001$)
Prendergast et al. (2017a)	126 participants (75 females) aged between 18–37 years with normal hearing thresholds (≤ 20 dB HL at 0.5–8 kHz)	Band-pass filtered clicks with a bandwidth from 1.5–4 kHz were presented at 80- and 100- dB peSPL at a rate of 11 clicks/s. Active electrodes were placed at the high forehead (Fz), the seventh cervical vertebra (C7), and the left and right mastoids (M1)	Noise exposure did not predict ABR wave I amplitudes at 80 dB peSPL (r = −0.07, $p > 0.05$) and 100 dB peSPL levels (r = −0.1, $p > 0.05$)	Females had larger ABR wave I amplitudes than males at 100 dB peSPL
Grose et al. (2017)	61 participants (29 females) aged between 18–35 with normal hearing as defined by hearing thresholds of ≤ 20 dB HL at 0.25–8 kHz. Participants were divided into two groups: the experimental group (n=31; had exposure to recreational noise) and the control group (n = 30; minimal exposure to recreational noise)	Clicks were presented at 95- and 105- dB ppeSPL at a rate of 7.7 clicks/s. An electrode montage of the ear-canal electrode (Tiptrode) as the inverting electrode was used for the test ear; the non-inverting electrode was placed midline on the high forehead and the ground electrode between the eyebrows	For both 95- and 105- dB ppeSPL presentation levels, the experimental group had lower ABR wave I amplitudes compared to the control group, however, the differences in ABR wave I amplitudes across both groups were not statistically significant (p = 0.67)	Males had significantly smaller ABR wave I amplitudes in both groups compared to females
Prendergast et al. (2018)	30 female participants aged 19–34 with normal hearing as defined by hearing thresholds of ≤ 20 dB HL at 0.25–8 kHz. Participants were divided equally into two groups based on lifetime noise exposure: the low-noise group (n = 15) and the high-noise group (n = 15)	Band-pass filtered clicks with a bandwidth of 0.1–1.5 kHz were presented at 80 dB nHL at a rate of 11 clicks/s. Two different electrode montages were used: mastoid electrode and canal tiptrode	Although the low-noise group had smaller ABR wave I amplitudes across both electrode montages compared to the high-noise group, the differences in ABR wave I amplitudes were not statistically significant ($p > 0.05$)	Not applicable
Valderrama et al. (2018)	74 participants (37 females) aged between 29–55 years. 84% of participants had normal hearing thresholds defined as ≤20 dB HL from 0.25–6 kHz	108.5 peSPL clicks using two reference electrode montage setups: ipsilateral mastoid (Fz-Tp9/Tp10) and ipsilateral ear canal (Fz-TIP)	After controlling for sex, the amplitudes of waves I, III, and V of ABR were smaller by 43.1, 60.7, and 45.4% respectively for participants with the 10% highest lifetime noise exposure units using Fz-Tp9/Tp10 electrode configuration compared to subjects with the lowest 10% lifetime noise exposure units. After controlling for sex and using the Fz-TIP electrode configuration, the amplitudes of waves I, III, and V of the ABR were smaller by 43.4, 63.7, and 41.1% respectively for participants with 10% highest lifetime noise exposure units compared to those with the lowest 10% lifetime noise exposure units Given all participants with various noise exposures, noise exposure was a significant predictor of ABR wave I amplitudes using Fz-Tp9/Tp10 montage (p = 0.0038) and Fz-TIP montage (p = 0.0215)	Males exhibited smaller ABR wave I amplitude compared to females

(Continued)

TABLE 3 | Continued

Study	Participants	ABR recording parameters	Outcomes	Sex-specific findings
Skoe and Tufts (2018)	55 participants (41 females) aged between 18–24 years were divided into two groups based on lifetime noise exposure: the low-exposure group (n = 29) and the high-exposure group (n = 26). All participants had normal hearing thresholds defined as ≤ 25 dB HL from 0.25–8 kHz	Clicks were presented at 75 dB nHL at eight presentation rates of 3.4, 6.9, 10.9, 15.4, 31.25, 46.5, 61.5, and 91.24 clicks/s. The non-inverting electrode was placed on the central vertex of the head (Cz), the inverting electrode was placed on the right earlobe (A2), and the ground electrode was placed on the forehead	No statistically significant difference in ABR wave I amplitude across different click rates between the low-exposure and high-exposure groups for either the peak-to-baseline wave I measure ($p = 0.73$) or the peak-to-trough wave I measure ($p = 0.88$). However, there was a trend of slightly smaller ABR wave I amplitudes for the high-noise exposure group compared to the low-exposure group across all click rates except for the 91.24 clicks/s	No statistically significant difference in ABR wave I between males and females across both the peak-to-baseline wave I measure and the peak-to-trough wave I measure. However, females had a trend of higher ABR wave I amplitudes compared to males in the peak-to-trough wave I measure, but not in the peak-to-baseline wave I measure
Couth et al. (2020)	137 participants (66 females) aged between 18–27 years. Participants were divided into two groups: musicians (n = 76) and non-musicians (n = 47). All participants had normal hearing thresholds defined as ≤ 20 dB HL from 0.25–8 kHz except for 4 participants who had mild hearing loss (hearing thresholds between 25–40 dB HL)	Clicks were presented at a level of 60 dB HL and 80 dB HL using a click rate of 11.1/s. A single-channel vertical montage configuration was used with the active electrode placed at Fz (high forehead), the reference electrode on the ipsilateral mastoid, and the ground electrode on the contralateral mastoid	Both musicians and non-musicians with high noise exposure exhibited statistically similar ABR wave I amplitudes ($p > 0.05$) compared to low-noise musicians and non-musicians respectively using both 60 and 80 dB nHL stimuli. There was a trend of non-significantly smaller ABR wave I amplitudes across high noise participants in both the musician and non-musician groups compared to their low-noise counterparts in both groups using the 60 dB nHL stimulus level	The authors did not control for the sex of participants in the analyses of ABR wave I amplitudes
Bramhall et al. (2021)	79 young audiometrically-normal participants (defined as having hearing thresholds of ≤ 20 dB HL from 0.25–8 kHz) aged 19–35 were divided into 3 groups: military veteran high noise ($n = 30$, 6 females), military veteran medium noise ($n = 18$, 10 females), and non-veteran control ($n = 31$, 17 females)	4 kHz tone bursts were presented at 90, 100, and 110 dB peSPL and a rate of 11.1/s. Ipsilateral ear canal montage was used	The posterior probability that the mean ABR wave I amplitude is greater for non-veteran controls than for high noise veterans at stimulus levels of 90, 100, and 110 dB pe- SPL was 94, 71, and 51%, respectively	No sex-specific noise exposure effects on ABR wave I amplitudes were found in all subgroups

of wave 1 of the ABR as documented in **Table 2**. The maximum age-related decline in wave 1 amplitude ranged between 70 and 90% (Sergeyenko et al., 2013; Parthasarathy and Kujawa, 2018), which is generally greater than that seen in studies investigating the effect of noise exposure in young animals (summarized in **Table 1**). This difference could be explained by the fact that age-related OHC loss had occurred in older animal subjects (which was not the case in young noise-exposed animals) especially in basal cochlear regions as documented by studies such as Sergeyenko et al. (2013), Liberman et al. (2014), Fernandez et al. (2015), and Parthasarathy and Kujawa (2018). Moreover, it is possible that aging and noise exposure result in different degrees of synapse and ANF loss depending on cochlear location and spontaneous rate level.

Since the ABR wave 1 amplitudes evoked by frequency-specific tone bursts are highly dependent on basal cochlear generators, as data from guinea pigs have shown (Eggermont, 1976), age-related basal OHC loss may further decrease the magnitude of the ABR wave 1 and thus obscure the effect caused by CS. It is worth pointing out that the ABR wave 1 amplitude reductions were seen to take place across all stimulation frequencies (i.e., low- and high-frequency tone bursts) in the animal studies summarized in **Table 2**. Based on this assumption, the pure effect of CS on the ABR wave 1 amplitude evoked by frequency-specific tone bursts can therefore only be determined once age-related basal OHC loss has been controlled for. However, computational modeling data from Verhulst et al. (2018a) suggest that OHC loss may have a limited impact on ABR wave 1 amplitudes for stimuli of 90 dB peSPL since the response growth of the OHCs is linear at high stimulus intensities. The computational modeling found that OHC loss even slightly increased ABR wave 1 amplitude for stimulus levels above 90 dB peSPL (Verhulst et al., 2018a). Moreover, Buran et al. (2022) also showed that accounting for cochlear gain loss (based on pure tone thresholds or distortion product otoacoustic emissions) in a computational modeling algorithm had a small effect on synapse predictions generated by the model from the ABR wave I amplitude measurements.

A strong correlation has been reported between the proportion of age-related synapse loss and ABR wave 1 amplitude in mice (Sergeyenko et al., 2013; Parthasarathy and Kujawa, 2018). **Figure 3A** illustrates the relationship from the results of Sergeyenko et al. (2013). It is important to point out that in this correlation analysis age-related OHC loss was never accounted for, and thus, the reductions in the ABR wave 1 amplitudes could be confounded by age-related threshold shifts. Further research is necessary to establish the effect of OHC loss on ABR wave 1 amplitude reduction secondary to CS (for the reasons discussed above) in order to establish whether ABR wave 1 amplitude may be a robust proxy measure of age-related CS with/without accounting for OHC loss.

Human Studies

Otologically normal older adult humans have consistently been shown to exhibit smaller ABR amplitudes for waves I to V compared to their younger counterparts (Rowe, 1978; Maurizi et al., 1982; Allison et al., 1983; Costa et al., 1991; Konrad-Martin et al., 2012; Grose et al., 2019; Johannesen et al., 2019; Grant et al., 2020). **Figure 3B** shows the ABR wave I amplitude as a function of age in five different human studies (redrawn from Bramhall, 2021). An age-related decrease in the ABR amplitude measured at 110 dB peSPL at low click rates (i.e., 11 clicks/second) has been estimated at 38, 43, and 34% reduction for waves I, III, and V respectively for audiometrically normal-hearing individuals. This translates into 9.5, 10.8, and 8.5% amplitude reduction per decade for waves I, III, and V respectively (Konrad-Martin et al., 2012). The authors accounted for age-related increases in the audiometric thresholds, and thus the reduction in ABR wave I may not be attributed to OHC loss.

Bramhall et al. (2015) investigated the effect of age on ABR wave I amplitude by recruiting 57 adults (35 females) aged 19–90 with average pure tone audiometric thresholds at 0.5, 1, 2, and 4 kHz ranging between −1.25 to 38.75 dB HL. The ABR wave I amplitudes obtained using a 4 kHz tone burst presented at 80 dB nHL at a rate of 13.3/second were not influenced by the sex of the participants in the statistical model. After controlling for audiometric threshold loss, ABR wave I amplitude was found to decrease by about 17.8% per decade. Buran et al. (2022) provided a re-analysis of the Bramhall et al. (2017) data ($n = 64$; age range: 19–35; summarized in **Table 3**). After the potential confounds of sex and OHC function (as reflected by distortion product otoacoustic emission levels) were accounted for, ABR wave I amplitude measured at 110 dB peSPL was found to decrease by about 6.1% per decade.

Carcagno and Plack (2020) attempted to minimize the contribution of basal cochlear generators to ABR wave I (Eggermont and Don, 1978), which may be reduced by the effects of age, by band-pass filtering the click stimulus at 0.35–3 kHz and by presenting the click in a high-pass masking noise of 3.5–8 kHz (study summarized in **Table 4**). The authors reported an age-related reduction in wave I amplitude when high-pass masking noise was employed, at a rate of 12% reduction per decade (ages of subjects ranged from 18–70 years), with clicks presented at 80 dB p-peSPL. However, no age-related reduction was seen at 105 dB p-peSPL. This is the opposite pattern to that expected based on CS affecting low-SR fibers. In contrast, they observed an age-related wave I reduction of 17% per decade when no masking noise was used at 105 dB p-peSPL click level (but no reduction at 80 dB p-peSPL) even when controlling for high-frequency hearing loss in the statistical model. This latter result is consistent with CS in high-frequency cochlear regions (i.e., above the 3.5 kHz cut-off of the high pass masker). It is worth highlighting that this sort of masking paradigm has not been investigated in animal models of CS, so this approach has not been validated.

Auditory Brainstem Response Wave I: Combined Effects of Noise Exposure and Aging

Animal Studies

Fernandez et al. (2015) reported that the ABR wave 1 amplitude in 88-week old CBA/CaJ mice exposed to the noise of 8–16 kHz at 100 dB SPL for 2 h at 16 weeks of age was 35, 65, and 80% smaller compared to 88-week old unexposed counterparts, 24-week-old young exposed animals, and 24-week-old young unexposed

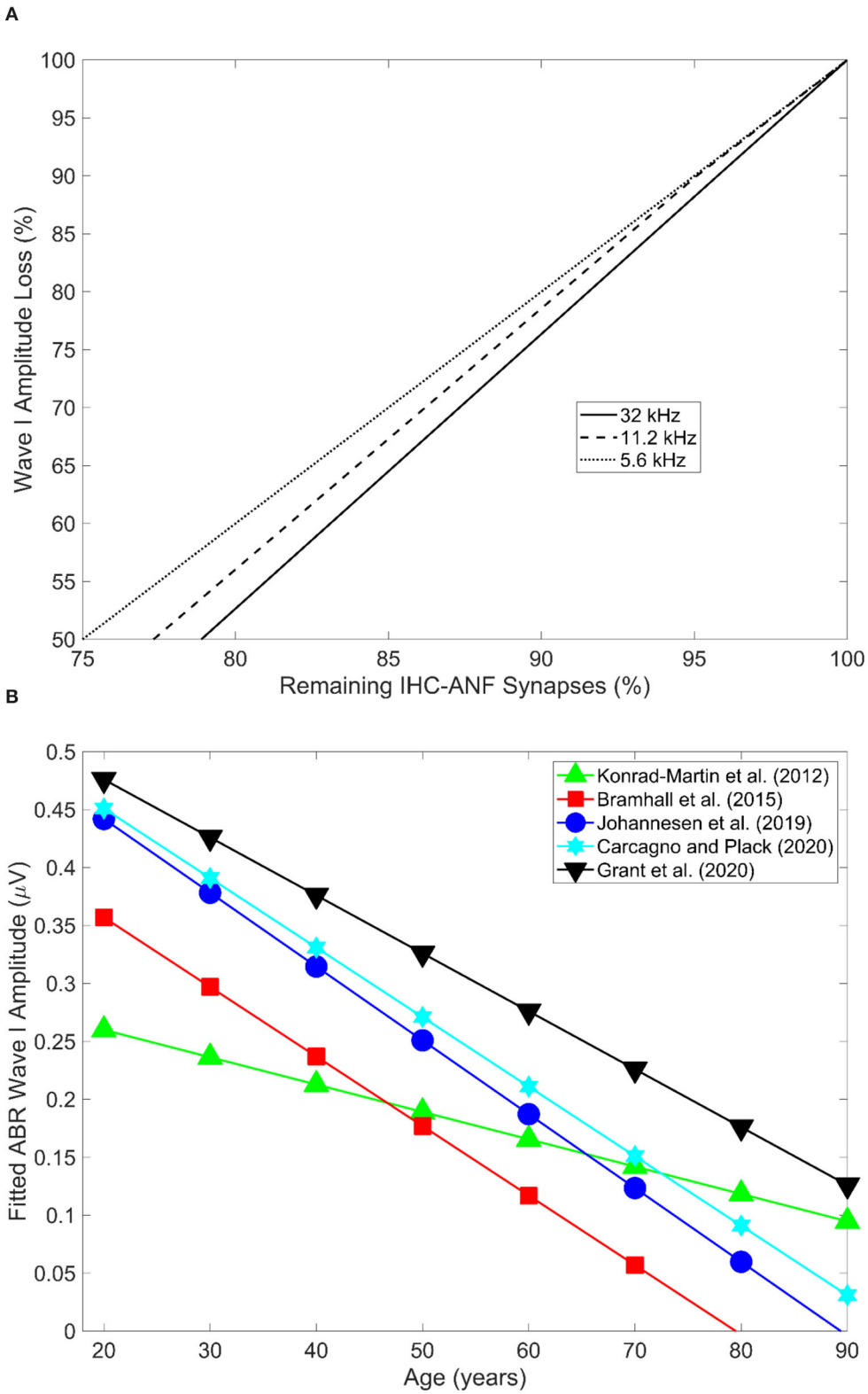

FIGURE 3 | (A) Shows the relation between age-related decline in wave 1 amplitude and remaining IHC-ANF synapses as estimated in the 5.6, 11.2, and 32 kHz cochlear regions in CBA/CaJ mice. Redrawn from the data reported in panel D of Figure 5 in Sergeyenko et al. (2013) using the online tool of WebPlotDigitizer version 4.5 (Rohatgi, 2021). **(B)** Illustrates ABR wave I amplitude as a function of age across five different human studies. Redrawn from the data reported in Figure 4 in Bramhall (2021) using the online tool of WebPlotDigitizer version 4.5 (Rohatgi, 2021).

TABLE 4 | Summary of the findings of key studies that investigated the combined effects of aging and noise exposure on wave I of ABR in humans. Data reported were either explicitly mentioned in the manuscript text or were derived from the relevant figures in the respective publications using the online tool of WebPlotDigitizer version 4.5 (Rohatgi, 2021).

Study	Participants	ABR Recording Parameters	Outcomes	Sex-specific findings
Valderrama et al. (2018)	74 participants (37 females) aged between 29–55 years. 84% of participants had normal hearing thresholds defined as ≤20 dB HL from 0.25–6 kHz	108.5 peSPL clicks using two reference electrode montage setups: ipsilateral mastoid (high forehead (Fz)-Tp9/Tp10) and ipsilateral ear canal (high forehead (Fz)-TIP)	After controlling for sex, amplitudes of wave I of ABR were smaller by 43.1% and 43.4% for participants with the 10% highest lifetime noise exposure compared to participants with the 10% lowest lifetime noise exposure using both the Fz-Tp9/Tp10 and the Fz-TIP electrode configuration respectively. Given all participants with various noise exposures, noise exposure was a significant predictor of ABR wave I amplitudes using Fz-Tp9/Tp10 montage ($p = 0.0038$) and Fz-TIP montage ($p = 0.0215$) The authors did not control for multiple comparisons, and the effect of noise exposure on the ABR wave I amplitude would not stay significant if the alpha level was adjusted for multiple comparisons of outcomes obtained using both electrode montages The effect of age was not considered in the analysis of ABR wave I data in relation to lifetime noise exposure, however, the authors argued that the reduction in the ABR wave I amplitude could be at least partially explained by the fact that middle-aged participants who were involved in the study tend to have age-related smaller ABR wave I amplitudes compared to younger participants	Males exhibited smaller ABR wave I amplitude compared to females
Prendergast et al. (2019)	156 participants aged 18–60 with hearing thresholds ≤20 dB HL up to 4 kHz and ≤30 dB HL at 8 kHz	100 dB peSPL clicks using the reference electrode montage of right (Fz-M1) and left (Fz-M2) mastoids	Neither age nor noise exposure had statistically significant effects on ABR wave I amplitude ($p > 0.05$). The Pearson's correlation coefficient between ABR wave I amplitude and age was−0.08	The authors did not report differences in the ABR wave I amplitude in relation to the sex of participants nor did they control for it in their analysis
Johannesen et al. (2019)	94 participants (64 females) aged 12–68 with hearing thresholds ≤20 dB HL at 0.5–4 kHz and ≤ 30 dB HL at 6–8 kHz	90–110 dB peSPL clicks using the reference electrode montage of the high forehead (Mastoid (M)-Fz)	Older participants had significantly lower wave I growth rates (for males $p = 0.034$; for females $p = 0.00013$). No effect of noise exposure on wave I growth was found (for males $p = 0.2$; for females $p = 0.83$). However, there was a trend of non-significantly smaller ABR wave I growth rates as a function of noise exposure for males only	The correlation between age and ABR wave I growth rates were stronger (i.e., more negative) in females compared to males
Carcagno and Plack (2020)	102 participants from three age groups: young (aged 18–39), middle-aged (aged 40–59), and older adults (aged > 60). All participants had hearing thresholds <20 dB HL at 0.125–2 kHz and <40 dB HL at 4 kHz	High level (105 dB p-peSPL) and low level (80 dB p-pe SPL) click in quiet and in high pass masking noise. The reference electrode montages used were ipsilateral earlobe (high forehead HF – ipsilateral earlobe IERL) and ipsilateral tiptrode (HF- ipsilateral tiptroad ITPR)	The ratio of wave I amplitude at high to low click levels was significantly decreased as a function of age (but no noise exposure) by a mean of about 12.6% per decade for the in-quiet ABR condition For the ABR in-noise condition, Wave I amplitude decreased as a function of age (but no noise exposure) by a mean of about 9.5% per decade using the low-level stimulus	Before controlling for sex, ABR wave I amplitudes in both the quiet and high-pass noise conditions were significantly larger for females compared to males at high-level stimuli

mice respectively. These findings imply that noise exposure at a young age in CBA/CaJ mice may cause a further reduction in the amplitude of the ABR wave 1 as animals become older (compared to unexposed aged counterparts). The authors have shown that a slower rate of IHC-ANF synapse loss as a result of aging has occurred in cochlear regions with the most CS due to noise exposure (compared to control cochleae without noise exposure). This is consistent with our saturative noise exposure-aging CS model which proposes the vulnerability of low- and medium-SR ANFs only. Nonetheless, this 35% decrease in the ABR wave 1 amplitude in exposed older mice (compared to unexposed older counterparts) may stem from the fact that the ABR wave 1 amplitude may be influenced by other noise- and age-related factors that were not controlled for such OHC and IHC loss.

Möhrle et al. (2016) reported that pre-noise-exposed middle-aged (6–10 months) and older (19–22 months) rats exhibited a 40% smaller amplitude of wave 1 compared to pre-exposed young (2–3 months) rats. However, no further significant decrease in the amplitude of wave 1 of ABR in post-exposed middle-aged and older rats was noted compared to their pre-exposed middle-aged and older subject counterparts (animals were exposed to 8–16 kHz broadband noise at 100 dB SPL for 2 h). The key difference in methodology between Fernandez et al. (2015) and Möhrle et al. (2016) is that the animals in the Möhrle et al. (2016) study were not exposed to noise and then aged. Rather, they were aged and then noise exposed. In line with the patterns of synapse loss across the different age groups in this study (as discussed earlier in the histopathological section), the authors hypothesized that, as most vulnerable ANFs are lost as a result of aging, little further reduction in the amplitude of wave 1 of ABR is seen when noise exposure is added to middle-aged and older animals. This is consistent with our saturative model of CS which suggests that when only low- and medium-SR ANFs are vulnerable to noise exposure and aging, less CS loss may occur once the majority of vulnerable IHC-ANF synapses have been lost.

Although Fernandez et al. (2015) and Möhrle et al. (2016) employed different rodent species, with major methodological differences as highlighted above, their findings shed light on the potentially different patterns of noise-induced CS when noise exposure occurs at a young or old age. These differences should inform future human studies investigating the interaction of aging and noise exposure.

Human Studies

The contribution of both noise exposure and aging to the amplitude of ABR wave I in humans with normal/near-normal hearing was investigated by some studies, which have reported mixed results. **Table 4** summarizes the methods and outcomes of these studies. Only Valderrama et al. (2018) reported that lifetime noise exposure may exacerbate an age-related decrease in the amplitude of wave I of the ABR. In contrast, other studies which considered the effects of noise exposure and aging found no correlation between lifetime noise exposure and ABR wave I amplitude (Prendergast et al., 2019; Carcagno and Plack, 2020). Similarly, Johannesen et al. (2019) reported no significant correlation between lifetime noise exposure and ABR wave I amplitude growth.

Several explanations have been proposed to justify the lack of consistency in the findings of the ABR wave I in relation to detecting CS across the different human studies. For instance, Bramhall et al. (2019) stated that the between-subject factors, which are difficult to control in human research, include the type (e.g., recreational vs. occupational/firearm noise) and duration of noise exposure as well as the tools used to retrospectively quantify them. Moreover, it could be difficult to rule out the presence of CS in the human control groups recruited based on self-reports of lifetime noise exposure. This is because noise exposure history is usually quantified using self-report questionnaires that primarily rely on subjects' ability to recall their history of noise exposure, which may not be optimally reliable and accurate (Bramhall et al., 2019). Another major concern with regards to the use of the ABR wave I amplitude is its potential lack of sensitivity to detect CS in humans due to the possibility that low-and medium-SR ANF responses may not contribute to ABR wave I amplitude (Versnel et al., 1990; Bourien et al., 2014). Rather, high-SR ANF activity may primarily dominate the ABR wave I amplitude (Bourien et al., 2014).

It has also been hypothesized that a noise-induced decrease in the amplitude of wave I of the ABR in normal-hearing humans could be so marginal that the current ABR wave I techniques may not be sensitive enough to detect it (Hickox et al., 2017). Prendergast et al. (2018) estimated that the coefficient of variation (CoV) of the ABR wave I amplitude was comparable to the wave V amplitude (i.e., CoV $<$ 0.35). This may be in favor of detecting the effect of noise exposure on the ABR wave I amplitude. However, if this variance does not directly relate to noise exposure, then many hundreds of participants may be needed to detect small noise-induced changes, even at a group level.

Both Prendergast et al. (2018) and Guest et al. (2019b) estimated that the amplitude of wave I in young normal-hearing adults exhibits high test-retest reliability (intraclass correlation coefficient of 0.85). So by assuming that humans exhibit a similar proportion of synapse loss as the non-human primates of macaque monkeys (i.e., up to 27%), a reduction in the ABR wave I amplitude should be evident in humans in longitudinal studies. However, data from guinea pigs suggests that some cochlear synapses damaged following noise exposure were partially repaired (Song et al., 2016). A similar effect could happen in humans, and thus ABR wave I amplitude recovers to some extent. This recovery may also be variable across humans, which adds a further source of variability in the measurement of ABR wave I amplitude in CS studies. It should also be noted that humans could exhibit different genetic susceptibility to noise- and age-related CS. Hence, this could be another major source of variability that may influence ABR wave I amplitude reductions.

Finally, since both noise exposure and aging are thought to be associated with worse hearing thresholds in the extended high frequency (EHF) range (Matthews et al., 1997; Somma et al., 2008; Liberman et al., 2016; Bramhall et al., 2017), ABR wave I amplitude reduction may be confounded by the involvement of basal high-frequency cochlear generators such that smaller

ABR wave I amplitude is recorded secondary to basal OHC loss (Eggermont and Don, 1978). As discussed earlier, it is important to establish the extent to which hearing threshold loss affects ABR wave I reduction, especially at high stimulus levels, in order to determine the efficacy of ABR wave I amplitude as a proxy measure of CS in the presence of noise-induced or age-related threshold elevations.

Auditory Brainstem Response Wave I:V Amplitude Ratio

In addition to the amplitude of wave I of the ABR, other electrophysiological objective metrics have been used to assess CS in both animal and human research. For instance, the ratio of ABR wave I amplitude to wave V amplitude (wave I:V amplitude ratio) is thought to reflect the compensatory central gain that is hypothesized to take place as a result of the ANF deafferentation (Schaette and McAlpine, 2011). As a result, the amplitude of wave V could remain the same (as a result of central neural compensation) or even increase (in case of over-compensation), hence reflecting increased neural activity at the level of the mid-brain where wave V is generated. This may therefore translate into tinnitus and hyperacusis in humans (Gu et al., 2012; Hickox and Liberman, 2014). A potential limitation with the use of ABR wave I:V amplitude ratio as a proxy tool to detect and quantify CS is that the degree of central gain in response to reduced peripheral input (as indicated by wave V amplitude) may vary. This means that two individuals with identical ABR wave I amplitudes could have different wave I:V ratios depending on the degree of central gain.

It is important to note that the wave I:V amplitude ratio was found to exhibit high test-retest reliability in young normal-hearing adults (Prendergast et al., 2018). This suggests that this synaptopathy metric is probably still worth considering in future research. However, as described above in the discussion of wave I amplitude, it is not clear whether the wave I:V amplitude ratio is sensitive enough to detect and quantify CS cross-sectionally.

Auditory Brainstem Response Wave I:V Amplitude Ratio: Noise Exposure

The effect of noise exposure on the ABR wave I:V amplitude ratio is inconsistent across the literature. On the one hand, a few studies documented evidence for the central gain hypothesis such that no change to the amplitude of wave V was found while the amplitude of wave I was decreased in young human and rodent subjects with a history of noise exposure (Schaette and McAlpine, 2011; Hickox and Liberman, 2014; Bramhall et al., 2017). Megarbane and Fuente (2020) reported that a smaller wave I:V amplitude ratio is associated with worse SPiN performance (which is considered as a potential perceptual consequence of CS) in one ear only of audiometrically normal young adults with variable self-reported SPiN abilities. On the other hand, Guest et al. (2017) and Prendergast et al. (2017a) reported no evidence of a smaller wave I:V amplitude ratio in noise-exposed young normal-hearing human subjects compared to controls with minimal noise exposure. Grose et al. (2017) found a significantly smaller wave I:V amplitude ratio in subjects with high noise exposure compared to low-noise control subjects. However, the reduction in wave I:V amplitude ratio was not correlated with tinnitus, and primarily occurred due to a reduction in wave I amplitude alongside no statistically significant change in wave V amplitude.

Auditory Brainstem Response Wave I:V Amplitude Ratio: Aging

In older CBA/CaJ mice with already documented basal OHC loss, Sergeyenko et al. (2013) reported a decreased amplitude of wave 1 of ABR with no evidence for reduced wave 5 amplitude, thus the authors suggested that the ratio of wave 1:5 amplitudes may decrease as a function of age. Verhulst et al. (2016) predicted that high-frequency sloping sensorineural hearing loss, typically accompanying ARHL (and potentially associated with noise exposure), may contribute to a smaller ABR wave I:V amplitude ratio when ABR click stimuli are used. This is because damage to basal cochlear generators may reduce wave I amplitude but have a much smaller impact on the amplitude of wave V (Eggermont, 1976; Eggermont and Don, 1978; Verhulst et al., 2016).

Normal-hearing older human adults were found to exhibit a diminished wave I:V amplitude ratio compared to their younger counterparts (Grose et al., 2019). Likewise, Carcagno and Plack (2020) reported no age-related decrease in the amplitude of wave V evoked using 105- and 80- dB p-peSPL clicks in quiet. In contrast, when clicks were presented at 80 dB p-peSPL with high-pass masking noise, the median of wave V reduction was estimated at 14% per decade. Interestingly, the changes in the ABR wave I and V amplitudes reported by Konrad-Martin et al. (2012) as indicated in **Figure 3B** show constant age-related decline in the amplitudes of both waves I and V evoked using 110 dB p-peSPL clicks in quiet. The data by Konrad-Martin et al. (2012) are therefore inconsistent with those reported by Grose et al. (2019) and Carcagno and Plack (2020) in quiet, and go against the hypothesis that a central compensation secondary to age-related peripheral neural deafferentation results in little change or even enhanced ABR wave V amplitude secondary to aging.

Auditory Brainstem Response Wave I:V Amplitude Ratio: Combined Effects of Noise Exposure and Aging

Möhrle et al. (2016) reported that after young and middle-aged rats were exposed to moderately loud noise, wave 1 amplitude significantly decreased while wave 5 amplitude remained intact in both age groups. Following a similar noise exposure pattern in older rats, both wave 1 and wave 5 amplitudes were reduced, which may indicate a decreased neuronal gain as a result of central auditory aging. These findings may explain the reduced ABR wave V amplitudes reported by Konrad-Martin et al. (2012) who tested military veterans (who were likely exposed to significant firearm noise), in that the ABR wave I:V amplitude ratio could be affected by central aging, apart from CS itself.

Recent human studies measured the wave I:V amplitude ratio as a function of age while taking into account noise exposure history (Valderrama et al., 2018; Prendergast et al., 2019; Carcagno and Plack, 2020). These studies found no evidence for reduced wave I:V in middle-aged and older adults. It is

worth pointing out that Valderrama et al. (2018) reported that middle-aged subjects with tinnitus had a statistically significantly lower wave I:V amplitude ratio compared to their non-tinnitus counterparts. However, the authors did not take into account the extent of audiometric threshold loss in their analyses, which could at least partially account for lower wave I:V amplitude ratios. These mixed findings add further uncertainty to whether the combined effects of aging and noise exposure result in CS-related compensatory central gain, and thus perceptually translate into tinnitus in humans.

Summating Potential to Action Potential Ratio

Animal Studies

The SP:AP ratio has also been used as a metric of CS. The normalization of the auditory nerve AP (related to wave 1 of ABR) to the SP of hair cells is hypothesized to help in distinguishing presynaptic and postsynaptic damage at the IHC-ANF synapse (Sergeyenko et al., 2013). In aging CBA/CaJ mice with documented synapse loss, a large SP:AP ratio was found after age-related OHC loss was accounted for statistically. CS, in the absence of OHC loss, may hence compromise AP of the auditory nerve, while the SP remains intact (Sergeyenko et al., 2013).

Human Studies

In human studies, the rationale for the use of the SP:AP ratio is to control for possible sources of measurement variability, such as differences in head anatomy (Liberman et al., 2016). Liberman et al. (2016) found that the SP:AP ratio was increased in noise-exposed young normal-hearing adults compared to low-noise controls, although this was primarily due to greater SP rather than smaller AP. Similarly, Grant et al. (2020) reported increased SP and decreased AP in audiometrically-normal adults with the worst word recognition scores (as defined by the lower 25^{th} percentile of word recognition scores) compared to their best-performing counterparts (i.e., those with the highest 75^{th} percentile of word recognition scores). Chen et al. (2021) studied the SP:AP ratio in older adults with a confirmed age-related threshold elevation. The authors found that AP amplitudes were significantly reduced in participants with SP:AP ratios that were deemed abnormal (i.e., $\geq$ 34%) while the SP amplitudes were similar across the normal and abnormal SP:AP groups. These findings provide evidence that CS may occur as part of ARHL.

It is worth highlighting the poor test-retest reliability of the SP:AP metric reported by Prendergast et al. (2018), at least for the click level of 115.5 dB peSPL tested in that study. Hence, the SP:AP ratio may not be reliable enough to determine the combined effects of aging and noise exposure on CS. Additionally, the use of SP:AP metric in older adults might be complicated by age-related hair cell loss, which will require careful control, as performed by Sergeyenko et al. (2013) in their mouse study. Finally, it may be worth considering the approach proposed by Kamerer et al. (2020) in future studies. This method employs validated Gaussian functions to estimate the SP and the AP and is thought to provide a more reliable measure than visual inspection and determination (Kamerer et al., 2020).

Envelope Following Response

The EFR is an objective auditory evoked potential characterized by neural responses that are phase-locked with the stimulus envelope modulation (Dolphin and Mountain, 1992). EFRs elicited with high-level stimuli with low modulation depths and high-frequency envelopes are thought to be sensitive to CS (Bharadwaj et al., 2014). This is because saturated high-SR fibers do not phase lock when presented with such stimuli, but low-SR fibers do (Bharadwaj et al., 2014, 2015; Shaheen et al., 2015; Verhulst et al., 2018b). Consequently, EFRs may be more sensitive to CS than ABR wave I amplitudes, not only because ABR measures are highly variable in humans and thus difficult to control for, but also because EFRs reflect phase locking to temporal envelopes in which low-SR fibers are strongly involved (Bharadwaj et al., 2014). Conversely, the computational model provided by Encina-Llamas et al. (2019) showed that the levels typically used to elicit EFRs (i.e., 70–80 dB SPL) may not be very specific to low-SR ANFs since, at these high intensities, the EFR responses are dominated by basal off-frequency high-SR ANFs that have not yet reached saturation. The computational model showed a minimal effect of subclinical OHC loss (which typically is associated with normal audiogram) on EFR amplitudes using the stimuli commonly presented at 70–80 dB SPL.

More recently, Vasilkov et al. (2021) provided evidence that the use of a stimulus with a rectangular envelope, with modulation rate, modulation depth, and duty cycles of 120 Hz, 95 and 25% respectively, presented at a fixed root mean square level of 70 dB SPL, may provide more sensitivity to CS while being minimally affected by co-existing OHC loss compared to sinusoidally amplitude-modulated tones that are commonly used. Moreover, Mepani et al. (2021) assessed the correlation between word recognition scores (words were presented in background noise) and EFR amplitudes using sinusoidally vs. rectangular-modulated carrier tones in otologically-normal adults aged 18–63. The sinusoidally amplitude-modulated tones were presented at 85 dB SPL using carrier frequencies of 1 or 8 kHz and were 100% amplitude-modulated at modulation frequencies of 128 or 750 Hz. The rectangular-modulated carrier tones were presented at 70 dB SPL at a modulation frequency of 120 Hz with a 25% duty cycle and 100% modulation depth. The word recognition scores were significantly positively correlated with EFR amplitudes evoked using rectangular-modulated tones, but not with sinusoidally modulated tones.

Envelope Following Response: Noise Exposure

Animal Studies

Shaheen et al. (2015) employed moderate stimulus levels (up to 90 dB SPL) with a carrier frequency of 11.3 kHz and 32 kHz and modulation frequencies ranging from 0.4–1.99 kHz to elicit EFRs in CBA/CaJ mice. EFR amplitudes were significantly reduced (by up to 55%) in noise-induced synaptopathic mice compared to non-synaptopathic controls at modulation frequencies near 1 kHz. For these high modulation frequencies, the EFR is thought to originate from the auditory nerve. This reduction, however, was not as large at lower modulation frequencies.

Human Studies

In humans, since EFRs obtained using a 1 kHz modulation frequency exhibit smaller amplitudes than in animal studies, lower modulation frequencies are often used which are thought to reflect neural generators from the midbrain rather than from more peripheral sources (Bharadwaj et al., 2015). For instance, Bharadwaj et al. (2015) assessed EFRs in young normal-hearing adults using a 4 kHz carrier tone modulated at 100 Hz, at a fixed level of 75 dB SPL with different modulation depths, presented in notched noise to restrict the cochlear region associated with the response. Subjects who showed the greatest decrease in EFR amplitude as a function of decreasing the modulation depth of the stimuli from 0 to −8 dB had the worst behavioral amplitude modulation thresholds ($r = 0.53$, $p = 0.008$). Moreover, the group of subjects who reported high past noise exposure had marginally significantly steeper positive EFR slopes (i.e., the slope of the line fit of EFR magnitudes in relation to modulation depths) compared to the low noise group ($p = 0.034$).

More recently, Bramhall et al. (2021) measured EFR amplitude in young audiometrically normal military veterans and non-veterans using a 4 kHz sinusoidally amplitude-modulated carrier tone presented at 80 dB SPL. The authors found that EFR amplitudes were 2.7, 2.5, and 3.4 dB smaller in the military veteran high-noise group at 100, 63, and 40% modulation depths respectively compared to the non-veteran control group. After adjustment for sex and OHC function, as reflected by the average distortion-product otoacoustic emission levels at 3–8 kHz, smaller EFR amplitudes were found at all modulation depths in high-noise military veteran male and female participants compared to their non-veteran counterparts.

Paul et al. (2017b) presented a 5 kHz carrier tone modulated at 86 Hz (with 0 dB modulation depth) at 75 dB SPL to two groups of young normal-hearing 18- and 19-year-old adults with and without significant noise exposure history. EFRs were measured both in quiet and in narrow band noise (NBN). The authors found reduced EFR magnitude for the high noise group compared with the low noise group. In a correction to the findings in the original publication, Paul et al. (2018) subsequently reported no statistically significant differences in the EFR amplitudes between the low and high noise groups across all measurement conditions ($p > 0.05$). Further studies such as those by Grose et al. (2017), Guest et al. (2017, 2018), Prendergast et al. (2017a) and Carcagno and Plack (2020) failed to find any significant relation between EFR amplitudes and lifetime noise exposure, tinnitus, or listening difficulties in young audiometrically normal adults. For the relation between EFR amplitudes and lifetime noise exposure, Grose et al. (2017) reported a p-value of 0.0664, while Guest et al. (2017) noted a correlation coefficient (r) of 0.01 between lifetime noise exposure and EFR amplitudes ($p = 0.94$). Prendergast et al. (2017a) found that the correlation coefficient (r) between lifetime noise exposure and EFR amplitudes obtained using 262 Hz pure tones was 0.08 ($p > 0.05$), while r was −0.16 ($p > 0.05$) when EFRs were elicited by 4 kHz pure tones. Guest et al. (2017) found that the tinnitus group had non-significantly lower EFR amplitudes than the control group ($p = 0.1$). Finally, Guest et al. (2018) reported similar EFR amplitudes across two groups of audiometrically-normal adults with and without listening difficulties ($p = 0.99$).

Paul et al. (2017a) assessed EFRs in young normal-hearing adults with and without chronic tinnitus using a 5 kHz carrier tone modulated at 85 Hz and presented at 75 dB SPL at three modulation depths of 0 dB (in quiet and in NBN), −2.5 dB with NBN, and −6 dB with NBN. In an erratum to the original publication, although no statistically significant difference in EFR amplitude was found between the tinnitus and control groups ($p = 0.207$), there was a trend toward lower EFR amplitudes for the tinnitus group compared to the control group (Roberts et al., 2018).

Other human studies based on computational simulation models of the peripheral and central auditory system predicted reduced EFR amplitudes in synaptopathic normal-hearing listeners (Verhulst et al., 2018a,b). The decreased EFR amplitudes were significantly associated with poor performance on psychoacoustic amplitude modulation tasks ($p < 0.05$; Verhulst et al., 2018a,b). Given the mixed findings using low modulation frequency stimuli in human studies, it is not clear whether the EFR at these frequencies is sensitive to noise-induced CS.

Envelope Following Response: Aging

Animal Studies

Progressive age-related CS has been associated with decreased EFRs to 1,024 Hz amplitude-modulated tones in older CBA/CaJ mice (Parthasarathy and Kujawa, 2018). This aging-EFR correlation was found significant across different tone levels and modulation depths. At lower modulation rates, which are dependent on more basal generators, decreased EFRs in older adults may arise not only from peripheral synapse loss but also from age-related deterioration in the central auditory system due to neural fiber loss and demyelination (Walton, 2010; Bharadwaj et al., 2014; Parthasarathy and Kujawa, 2018).

Lai et al. (2017) measured EFR amplitudes in young and aged Fischer-344 rats, using 8 kHz carrier tones modulated at frequencies of 45, 128, and 456 Hz and modulation depths ranging from 3.125% (−30 dB) to 100% (0 dB). The authors accounted for age-related peripheral hair cell and neural degeneration, which may manifest as poorer central neural responses, by adjusting the EFR stimulus level presented to the age groups so that the ABR amplitudes for these levels were similar. After this peripheral activation matching, the authors reported enhanced EFR amplitudes at 100% modulation depth (but not at 25% modulation depth) in the aged animals compared to their young counterparts. This was found when tones were modulated at 16–90 Hz (which are thought to generate EFRs originating from central auditory neural generators) were presented at 85 dB SPL. This age-related EFR amplitude enhancement suggests that older subjects had increased compensatory central gain as a result of decreased peripheral ANF neural activity.

To emphasize the differences in EFR while taking into account age-related central gain, the authors performed an additional "central" activation matching to the EFR stimuli. This was done by measuring the EFR amplitudes of old rats using 85

dB SPL tones that are 100% amplitude modulated at 45, 128, and 256 Hz with a carrier frequency of 8 kHz (which would stimulate the cochlear region with the least age-related changes in hearing thresholds). The median EFR amplitude in aged rats for each of the amplitude-modulated tones was measured. The authors then identified the EFR stimulus intensities to be used in the cental matching by measuring the EFR amplitudes in young rats using sinusoidally amplitude-modulated tones presented at 85–60 dB SPL (in 5-dB descending steps). The EFR stimulus intensity that produced equivalent central activation across the young and older rats was subsequently employed in EFR amplitude measurements. For both types of peripheral and central matching independently, no significant age-related differences in EFR amplitudes at different modulation depths and frequencies between the young and aged animals were reported, which suggests that peripheral and central auditory temporal coding was not different between the two age groups.

Human Studies

In humans, Prendergast et al. (2019) employed four low-frequency tones of 240–285 Hz to modulate a carrier frequency of 4 kHz at an intensity of 80 dB SPL in young and middle-aged audiometrically normal (up to 4 kHz) adults. The authors reported that participants' age did not predict EFR amplitudes (adjusted $r^2 = -0.004$, $p = 0.495$). Patro et al. (2021) measured EFR amplitudes in audiometrically normal adults using a carrier frequency of either 2 or 4 kHz modulated at a rate of 91.42 Hz presented either in quiet (70 dB SPL at modulation depths of −8 or 0 dB) or in notched-noise (presented at an overall level of 60 dB SPL at modulation depths of −8, −4, and 0 dB). For the 2 kHz carrier frequency, the oldest adults had significantly reduced phase-locking value (PLV) of the EFR at 0 dB modulation depth in quiet compared to their youngest counterparts ($p = 0.048$). The oldest group produced the lowest PLV compared to the middle-aged and youngest adult group for the carrier frequency of 4 kHz at modulation depths of 0 dB in quiet ($p = 0.031$) and −8 dB in noise ($p = 0.009$).

More recently, Vasilkov et al. (2021) found that EFR amplitudes evoked by rectangular modulated stimuli presented at 70 dB SPL at a modulation rate of 120 Hz, a modulation depth of 95%, and a duty cycle of 25%, were significantly reduced in older adults with suspected age-related CS ($p < 0.0001$). Moreover, the authors found that their single-unit ANF simulation model suggested that ANFs fired more synchronously with this type of EFR stimulus compared to the commonly used sinusoidally amplitude-modulated stimuli (Vasilkov et al., 2021).

Envelope Following Response: Combined Effects of Noise Exposure and Aging

Carcagno and Plack (2020) measured EFR amplitudes in young, middle-aged, and older adults using two carrier tones of 0.6 and 2 kHz, modulated at around 100 Hz using two modulation depths of 100 and 70%, embedded in pink noise (to minimize the contribution of high-SR fibers) and using band-pass noise at 3–8 kHz (to minimize the contribution of high-frequency cochlear regions). The authors reported a significant age-related reduction in EFR amplitudes using a 0.6 kHz carrier at both modulation depths, while no effect was noted for the 2 kHz carrier at either modulation depth. No correlation between EFR amplitudes and lifetime noise exposure was found for either 0.6 or 2 kHz carrier tones. These findings are consistent with earlier studies such as those by Leigh-Paffenroth and Fowler (2006), Grose et al. (2009), and Garrett and Verhulst (2019) which documented an age-related decline in electrophysiological measures of phase-locking at subcortical levels using modulation rates of about 100 Hz.

Given the above studies, there is some evidence that aging may degrade EFR amplitudes, potentially due in part to the deterioration of central auditory pathways in older adults. However, the evidence on the effect of noise exposure on EFRs has been generally mixed and inconclusive. It is not yet clear whether EFRs are sufficiently sensitive, at least using the currently used research paradigms in humans, to capture CS and peripheral ANF loss. This is because human studies employed much lower modulation frequencies to elicit EFRs, unlike animal studies which mainly used higher modulation frequencies that are believed to reflect the function of more peripheral auditory neural generators (Parthasarathy and Kujawa, 2018). Moreover, EFR amplitudes in the aged population may be influenced by enhanced central gain, central neural dysfunction, and high-frequency cochlear damage, which may add further ambiguity to identifying CS in the low–mid-frequency range (Lai et al., 2017). Furthermore, Hesse et al. (2016) suggest that EFRs could be primarily mediated by high-SR rather than low-SR fibers at high levels and may not hence be effective in the search for low-SR fiber loss.

Middle Ear Muscle Reflex

The MEMR, which in clinical terms is known as acoustic reflex (AR), is an objective measure of change in middle ear immittance that occurs as a result of an efferent feedback mechanism to the middle ear stapedial muscle in response to intense acoustic stimulation. Low- to medium-SR type I fibers may be involved in the afferent branch of the MEMR pathway (Kobler et al., 1992). Two types of MEMR approaches have been used in CS research: the standard tonal probe approach and the wideband probe approach. The standard tonal MEMR probe approach is widely used in clinical settings and measures middle ear admittance at one probe tone of 226 Hz or 1,000 Hz (Schairer et al., 2013). In contrast, the wideband probe MEMR determines middle ear admittance, power reflectance, and absorbance over a broad frequency range typically between 0.25 and 8 kHz (Schairer et al., 2013). Prendergast et al. (2018) and Guest et al. (2019b) reported that the MEMR thresholds obtained using the standard tonal probe approach exhibited high test-retest reliability in young audiometrically-normal human adults. This provides some promise to using the MEMR in the search for CS in humans.

Middle Ear Muscle Reflex: Noise Exposure

Animal Studies

In mice with a histologically verified noise-induced CS, MEMR thresholds obtained using wideband probe and broadband elicitors were significantly increased while MEMR growth functions (i.e. MEMR magnitudes as a function of elicitor level)

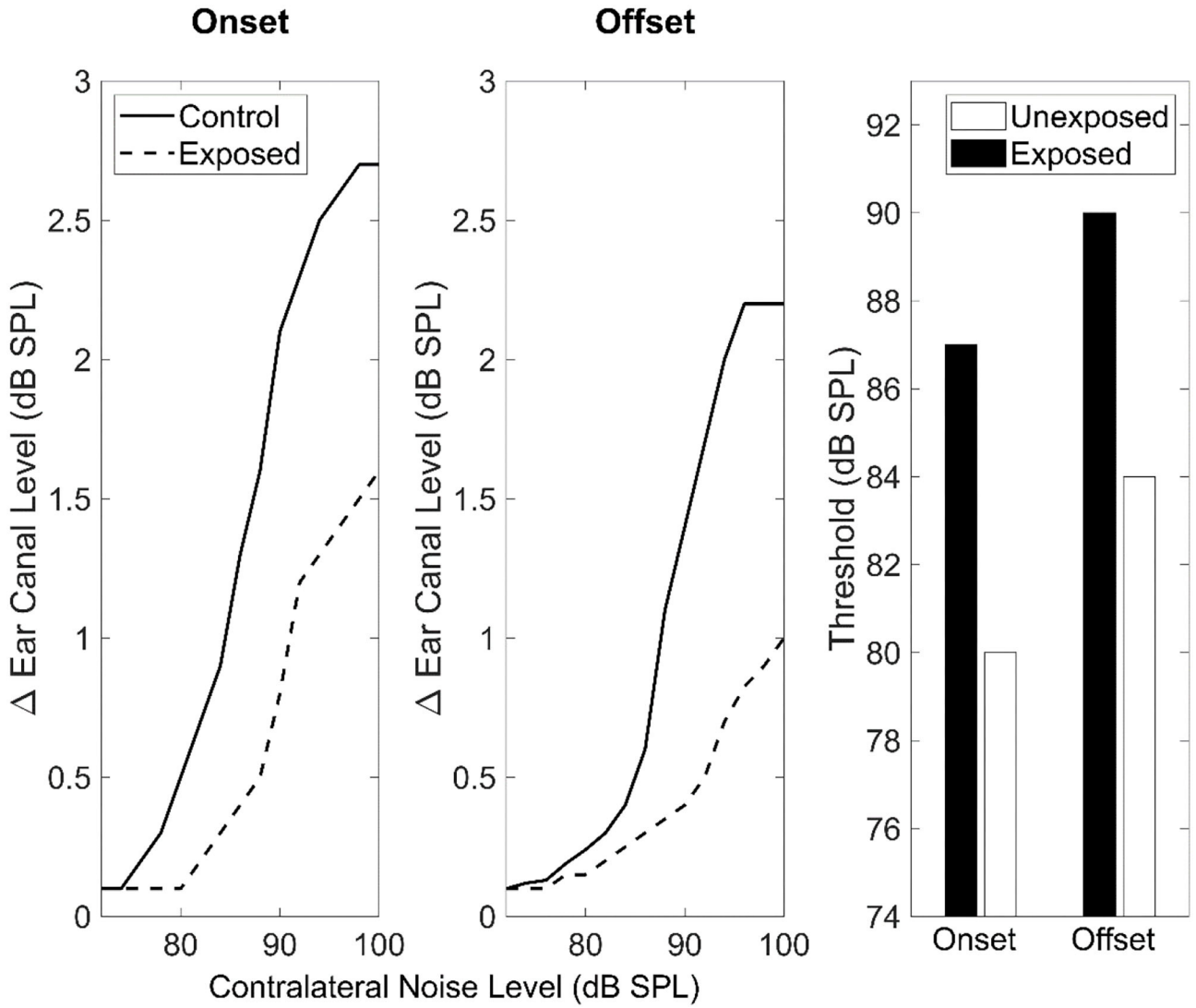

FIGURE 4 | MEMR thresholds and growth functions (expressed as the difference in-ear canal SPL as a function of contralateral noise level) in noise-exposed and control mice measured at stimulus onset and offset. A wideband chirp covering a range of 4–64 kHz was presented contralaterally. This figure is redrawn from the data reported in panels A, B, and C of Figure 7 in Valero et al. (2016) using the online tool of WebPlotDigitizer version 4.5 (Rohatgi, 2021).

were considerably decreased at frequencies corresponding to the affected cochlear regions compared to non-synaptopathic areas (Valero et al., 2016, 2018). Therefore, the MEMR has been suggested as a good proxy for CS (Bharadwaj et al., 2019). **Figure 4** shows a schematic representation of MEMR thresholds and growth functions in mice with verified CS compared to control mice respectively as measured at contralateral noise onset and offset (redrawn from Valero et al., 2016).

Human Studies

In humans, some recent studies have suggested a relation between MEMR amplitude and noise-induced CS. For instance, Shehorn et al. (2020) reported that high lifetime noise exposure is associated with lower ipsilateral broadband MEMR amplitude in normal-hearing young and middle-aged adults. Recently, Bramhall et al. (2022) measured the contralateral MEMR growth functions in 92 audiometrically-normal military veterans (who are typically exposed to firearm noise) and non-veterans aged 19–35 using a wideband probe and a broadband elicitor. The authors reported a trend of reduced MEMR growth functions in military veterans with high noise exposure compared to their non-veteran control counterparts. The mean difference in MEMR magnitude was lower by 0.29 dB in the veteran high noise group compared to the non-veteran control group. Other studies which involved normal-hearing young adults found a correlation between the presumed perceptual consequences of

CS, such as poorer speech perception in noise and tinnitus, and reduced MEMR strength using the wideband probe approach (Wojtczak et al., 2017; Mepani et al., 2019; Shehorn et al., 2020). In contrast, Guest et al. (2019a) failed to find an association between MEMR thresholds (using the standard tonal probe and elicitors) and noise exposure, tinnitus, and coordinate response measure (CRM) SPiN thresholds. Moreover, Causon et al. (2020) failed to document a relationship between lifetime noise exposure in young normal-hearing subjects and MEMR thresholds and growth functions obtained using the clinical standard probe tone of 226 Hz and tonal elicitors. These negative findings may be potentially explained by the lack of sensitivity of the clinically MEMR protocol (which employs tonal elicitors and 226 Hz probe tone) to detect CS compared to the wideband probe and broadband noise elicitors employed by the other studies (Causon et al., 2020; Shehorn et al., 2020).

Middle Ear Muscle Reflex: Aging

Earlier studies suggest increased MEMR thresholds in normal-hearing older adults compared to their younger counterparts when measured by the standard clinical probe tone approach using broadband elicitors, but not low-to-mid frequency tonal elicitors (i.e., 0.5, 1, and 2 kHz), after controlling for the differences in audiometric thresholds (Silman, 1979; Gelfand and Piper, 1981). Wilson (1981) reported that older adults may show higher MEMR thresholds using the standard clinical probe tone approach, not only using broadband noise elicitors but also using tonal elicitors of 4 kHz and 6 kHz. Moreover, MEMR growth has been observed to decrease as a function of age (Thompson et al., 1980). In contrast, Unsal et al. (2016) found no differences in either the MEMR thresholds (obtained by the standard clinical probe tone approach) using 4 kHz tonal elicitors, or the MEMR decay, between older and younger adults. The correlation between MEMR thresholds/growth functions and aging in the above studies could be at least partially explained by age-related declines in central auditory neural pathways (Ouda et al., 2015), which need to be accounted for in the investigation of age-related CS using MEMR measures.

Middle Ear Muscle Reflex: Combined Effects of Noise Exposure and Aging

MEMR thresholds and growth functions using broadband noise elicitors may have promise as a measure of synaptopathy given the studies discussed above. However, it is not yet known whether lifetime noise exposure compounds the effect of age on MEMR strength.

BEHAVIORAL PROXY MEASURES IN HUMANS

In this section, the evidence from human studies on noise exposure, aging, and the combined effects of noise exposure and aging using behavioral proxy measures of CS will be discussed.

Behavioral Proxy Measures in Humans: Noise Exposure

Based on the hypothesis that low- to medium-SR high threshold ANF fiber loss may affect speech perception at moderate-to-high levels (Liberman and Liberman, 2015), human studies have considered SPiN performance, and other proxy behavioral measures, concerning noise exposure in young normal-hearing adults. SPiN outcomes have been mixed and inconclusive (for reviews see Bramhall et al., 2019 and Le Prell, 2019).

Some studies have measured the effect of noise exposure on non-speech auditory psychoacoustic perceptual tasks in young normal-hearing adults. Measures such as interaural phase difference (IPD) discrimination, frequency and intensity difference limens, sound localization, and amplitude modulation detection have been used. Findings have been generally mixed and inconclusive. For instance, some studies reported that noise-exposed normal hearing adults exhibited poorer detection of temporal fine structure (e.g. discrimination of Gaussian noise from low-level noise with minimal envelope fluctuations) (Stone et al., 2008), worse amplitude modulation detection (Kumar et al., 2012; Stone and Moore, 2014; Verhulst et al., 2018b), and poorer IPD discrimination (Shehorn et al., 2020). In contrast, other studies failed to document a correlation between noise exposure and IPD discrimination, frequency, and intensity difference limens, sound localization, and amplitude modulation detection in young normal-hearing adults (Grose et al., 2017; Prendergast et al., 2017b, 2019; Yeend et al., 2017).

These mixed outcomes for behavioral proxy measures of CS in young noise-exposed humans with normal audiometric profiles could potentially be explained in three ways (Guest et al., 2018). Firstly, Noise-induced CS could not be as widespread in young normal-hearing adult humans as it is in rodent models. Secondly, the current behavioral measures in humans may not be particularly sensitive to CS. Based on signal detection theory, Oxenham (2016) showed that a synapse loss in humans up to 50% may not necessarily translate into measurable effects on behavioral tasks. Furthermore, the different behavioral tools used in human CS studies place variable sensory, perceptual, and central/cognitive demands (such as attention and memory), which likely contribute to inter-subject variability (Bramhall et al., 2019; DiNino et al., 2022). Thirdly, noise-induced CS in humans might not preferentially impair low- to medium-SR ANFs (as discussed in Section Histopathological and Neurophysiological Aspects: Noise Exposure). Moreover, low- to medium-SR ANFs might not have high thresholds in humans, consistent with evidence from non-human primates (Hickox et al., 2017). Hence, CS may not cause differential effects on performance as a function of stimulus level, as assumed by some measures.

Behavioral Proxy Measures in Humans: Aging

Audiometrically normal/near-normal older adults with no cognitive decline have consistently been shown to exhibit poorer SPiN performance using different types of speech stimuli and competing background noises compared to their younger

counterparts (Pichora-fuller et al., 1995; Kim et al., 2006; Füllgrabe et al., 2015; Vermeire et al., 2016; Babkoff and Fostick, 2017). Compromised temporal processing, which may arise due to age-related central neural degeneration as well as CS, has been suggested to explain the difference in performance (Gordon-Salant and Fitzgibbons, 1993; Füllgrabe et al., 2015; Babkoff and Fostick, 2017). It is worth highlighting that not all studies which found an age-related decline in SPiN performance controlled for cognitive performance when comparing outcomes to younger adults. While the effect of age-related CS on SPiN tasks cannot be ruled out, it is possible that age-related deterioration in the EHF (i.e., frequencies above the standard clinical range of 8 kHz) thresholds (Stelrnachowicz et al., 1989; Snell et al., 2002), central auditory processing (Caspary et al., 2008; Ouda et al., 2015) and cognitive decline (Humes and Dubno, 2009; Kamerer et al., 2019) may contribute to the observed differences. Moreover, the variability in audiometric hearing thresholds and OHC function was not controlled for in the studies investigating the age-related auditory perceptual deficits in audiometrically normal/near-normal adults as discussed above. This may partially influence SPiN/psychophysical outcomes in favor of the younger population, which generally has better OHC function and hearing thresholds.

Some studies have tried to isolate the effects of CS by measuring performance as a function of level, under the assumption that CS will differentially affect higher levels due to low- and medium-SR ANF loss. Prendergast et al. (2019) found that, for audiometrically normal adults, age did not predict performance on the CRM task in either the 40 and 80 dB SPL stimulus presentation conditions while hearing thresholds at 2 and 16 kHz were accounted for. However, older participants performed significantly better than their younger counterparts in the 40 dB SPL condition of the digits in noise (DIN) task while older age was associated with worse performance on the 80 dB SPL condition. This is in line with the hypothesis that older subjects with age-related CS affecting low- to medium-SR ANFs perform worse with higher-level SPiN stimuli, but not lower-level stimuli, compared to their younger counterparts. The effects of the hearing thresholds at 0.5 kHz and EHF threshold at 16 kHz were controlled for in two separate statistical models and they were shown to be significant predictors of DIN thresholds.

Carcagno and Plack (2021) measured CRM and DIN thresholds using low-pass filtered speech stimuli (at a cut-off frequency of 3 kHz) presented at low and high levels to audiometrically normal adults of various ages. The authors employed pink band-pass filtered noise at 3–8 kHz in both tasks to reduce the contribution of basal cochlear generators. No credible age-related declines were found in the CRM task (using both collocated and spatially separated maskers) or in the DIN task at either level. Likewise, Johannesen et al. (2019) attempted to isolate the effects of age-related CS by employing both sentences from the hearing in noise test (HINT) fixed at 65 dB SPL and disyllabic words at 50, 65, and 75 dB SPL, while the masking noise (which was either speech shaped noise SSN or the international female fluctuating masker IFFM) was varied adaptively. Authors found that age was a significant predictor of HINT thresholds using both SSN and IFFM maskers, but not of the disyllabic words in noise thresholds (using either masker). The effect of differntial speech level used in the HINT test was not a significant predictor of SPiN performance as a function of age, even after the variability in hearing thresholds across subjects is accounted for.

Patro et al. (2021) employed sentence target stimuli presented either as full-spectrum or lowpass filtered signal (presented at a fixed level of 75 dB SPL in both conditions) embedded in a speech masker of either the same or different F_0. The proportion of correct scores was measured in two spatial conditions: co-located (i.e., target and masker at 0° azimuth) and non-colocated (target and masker at ±15° azimuth). A significant age effect was reported for both conditions of the full-spectrum and lowpass-filtered speech target embedded with the same/different F_0 speech maskers, however, no significant interaction between the spatial condition and age group was found.

Age-related declines in performance in psychoacoustic tasks in audiometrically normal older adults are inconsistent across the literature. For instance, on the one hand, decreased performance on amplitude modulation tasks (He et al., 2008; Füllgrabe et al., 2015; Wallaert et al., 2016; Carcagno and Plack, 2021), IPD discrimination (King et al., 2014; Füllgrabe et al., 2015; Carcagno and Plack, 2021), gap detection thresholds for a tone in noise (Patro et al., 2021), and frequency discrimination (He et al., 1998; Clinard et al., 2010) has been found in older adults compared to their younger counterparts. On the other hand, data from Grose et al. (2019), Paraouty et al. (2016), Patro et al. (2021), Prendergast et al. (2019) and Schoof and Rosen (2014) (amplitude modulation detection), Carcagno and Plack (2021) and Patro et al. (2021) (low-frequency carrier IPD discrimination task), Prendergast et al. (2019) and Patro et al. (2021) (high-frequency carrier IPD discrimination task) and Bianchi et al. (2019) and Carcagno and Plack (2021) (for frequency discrimination) provide no evidence for age-related declines in these psychophysical tasks. This inconsistency in findings may be partly explained by the fact that not all studies accounted for the variability in hearing thresholds, EHF thresholds, cognitive factors, past musical training, as well as central auditory processing ability in the analysis of their psychoacoustic data.

A few studies have attempted to isolate the effects of age-related CS on psychoacoustic tasks by presenting the psychophysical stimuli at different levels such as those by Prendergast et al. (2019) and Carcagno and Plack (2021). Yet, the outcomes of these studies provide little evidence of poorer performance at higher stimulus levels.

Behavioral Proxy Measures in Humans: Combined Effects of Noise Exposure and Aging

A few recent studies have attempted to evaluate the combined effects of aging and lifetime noise exposure on SPiN tasks. For instance, Valderrama et al. (2018) found that SPiN performance (using the high cue LiSN-S test) in young and middle-aged normal hearing adults was neither predicted by their age nor by their lifetime noise exposure. Similarly, Johannesen et al. (2019)

showed that while noise exposure did not seem to influence the SPiN scores, older normal hearing subjects performed worse on a SPiN task involving words presented in steady and fluctuating noises compared to their younger counterparts. However, age (which ranged from 12 to 68 years in Johannesen et al., 2019 study) did not seem to influence the performance of participants in a different SPiN task involving sentences embedded in the same types of noises. Furthermore, Prendergast et al. (2019) and Carcagno and Plack (2021) reported that neither age nor lifetime noise exposure predicted the SPiN performance of subjects using the CRM task. However, the authors had conflicting findings concerning the effect of age using the DIN task, such that Prendergast et al. (2019) reported that older age was unexpectedly associated with better DIN thresholds at low stimulus levels while higher lifetime noise exposure was associated with better scores at high stimulus levels. In contrast, Carcagno and Plack (2021) found that neither age nor noise exposure had effects on DIN thresholds using their band-limited stimuli.

The evidence on the combined effects of aging and lifetime noise exposure on psychoacoustic tasks is sparse and inconclusive. Prendergast et al. (2019) and Carcagno and Plack (2021) have recently found that neither aging nor lifetime noise exposure was correlated with performance on a high-frequency carrier IPD task (Prendergast et al., 2019) and low-frequency carrier IPD task (Carcagno and Plack, 2021). Moreover, Carcagno and Plack (2021) found no interaction between lifetime noise exposure and aging on the amplitude modulation detection and frequency discrimination tasks. These inconsistent and mainly negative findings add further doubt to the sensitivity of these psychoacoustic tasks in detecting CS.

SUMMARY AND RECOMMENDATIONS FOR FUTURE RESEARCH

In summary, animal histopathological studies have shown that both noise exposure and aging result in a substantial, yet highly variable, degree of synapse and ANF loss across several species. Rodent studies on the combined effects of noise exposure and aging suggest that animals who experience intense noise exposure at a young age may exhibit substantial noise-induced CS, and then go on to exhibit further CS as they age. However, the impact of noise exposure on older animals tends to be reduced, suggesting a saturation-like effect.

In young adult humans, histopathological studies are still lacking on the effects of noise exposure on synapse loss. Recently, Wu et al. (2021) have confirmed noise-related ANF loss in middle-aged and older human subjects. With regards to aging, human temporal bone studies suggest an age-related loss of synapses and ANFs, but these could not ascertain whether the lost fibers were primarily low-to-medium-SR ANFs, as is the case in rodent models, due to the lack of methods for classifying ANFs based on their SR in humans. The current human temporal bone data seem to be consistent with a model that assumes that only a portion of synapses (perhaps those with low- and medium-SR ANFs) are vulnerable to aging and noise exposure. While noise exposure was associated with a reduction in ANFs for middle-aged adults, older adults, who had a reduced baseline number of ANFs, did not show an additional effect of noise exposure (Wu et al., 2021). There are two possible explanations for the observed effect: first, these older adults may have reached the maximum extent of synapse loss, due to the effects of age alone, thus no further CS has taken place due to noise exposure; alternatively, the older "unexposed" adults may have had considerable undocumented noise exposure that eventually resulted in a similar extent of CS compared to their "exposed" counterparts.

Animal studies have consistently shown that noise-induced and age-related synapse and ANF loss are related to reductions in objective metrics (i.e., ABR wave 1, EFR, and MEMR amplitudes). In humans, objective and behavioral measures have produced inconsistent outcomes in relation to noise-induced CS, with some studies showing effects consistent with CS and others not. It is worth pointing out that estimates of the effect of noise exposure on physiological proxy measures of CS vary, with some studies showing large effects and others showing small non-significant effects. Some of this variability may be due to variability in study design and the type of noise exposure (e.g., military noise vs. recreational noise) as discussed earlier. In contrast, age-related changes in objective (e.g., wave I of ABR, EFR, and MEMR) and behavioral metrics are generally consistent across the human literature. However, it is not clear whether these changes relate directly to the synapse loss or are brought about by the age-related changes that occur across the entire auditory neural pathways. Only a few behavioral studies have attempted to isolate the effects of CS by comparing outcomes across levels, and these have not shown any clear differential effects. Future research will also need to account for the age-related loss of basal hair cells when investigating electrophysiologic neural responses (e.g., wave I of ABR and EFR) as well as the effects of cognitive decline when measuring behavioral performance in older adults.

Most of the current evidence in humans is based on observational cross-sectional studies that involve proxy objective or behavioral measures. Future research may need to employ longitudinal study designs and focus on the development and employment of more sensitive objective and behavioral tools based on a gold-standard measure of CS in living humans that relies on more robust CS models derived from animal and human temporal bone data. In particular, wideband MEMR thresholds and growth functions when measured using broadband elicitors are promising as sensitive measures of CS in humans. It may also be critical to establish more sensitive estimation tools of lifetime noise exposure such as by developing noise exposure metrics validated to objective measures (e.g., dosimetry). The need to control for differences in genetic susceptibility to noise- and age-related CS may still be a challenge in future research studies.

Although we recognize that it may be difficult to disentangle and control for all the different factors that may influence peripheral neural auditory aging, we recommend that future research focuses on the effects of noise exposure and aging in combination, rather than in separation, by determining when in the human lifespan noise exposure has occurred and the rate of progression of CS in ARHL using both histopathological and proxy approaches. This could be potentially achieved by

controlling for past exposure to ototoxic substances and carefully screening and accounting for pathologic history, particularly some common chronic conditions among older adults that may affect peripheral hearing such as diabetes, blood hypertension, as well as genetic factors that may accelerate ARHL. Longitudinal study designs may be particularly useful in this regard, for instance studying cohorts of humans who are noise-exposed in occupational settings, compared to controls with a quiet lifestyle.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Hearing Impairment With Cognitive Decline Increases All-Cause Mortality Risk in Chinese Adults Aged 65 Years or Older: A Population-Based Longitudinal Study

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Background: Hearing impairment (HI), a highly prevalent sensory impairment affecting older adults, is a risk factor for cognitive decline. However, few studies examined the association between HI and all-cause mortality, and the role of different cognitive states on this relationship in Chinese older adults is poorly understood.

Methods: A total of 10,744 Chinese older adults aged 65 years or older were included in the 2011/2012 and 2014 cohorts from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), with the longest follow-up period lasting for up to 8 years. The presence of HI was identified by using a dichotomized metric of self-reported hearing status. All-cause mortality data were ascertained from interviews with family members or relatives of the participants. Cognitive function was evaluated by employing the modified Mini-Mental State Examination (MMSE), which consisted of seven subdomains (orientation, naming foods, registration, attention and calculation, copy figure, delayed recall, and speech and language). Kaplan–Meier survival curves were constructed to evaluate the different hearing states on overall survival. The risk of mortality over the follow-up period was estimated by using Cox proportional hazard ratios (HRs) models.

Results: A conspicuous probability was revealed in the survival relationship between hearing status and all-cause mortality for the total population ($p < 0.001$). Participants with HI had a higher risk of all-cause mortality (HR = 2.29, 95% CI: 2.16, 2.42), as compared with their counterparts without HI. The association was robust upon fully adjustment for potential confounders (HR = 1.07, 95% CI: 1.00, 1.14). Compared to HI participants with no cognitive impairment, HI patients with cognitive impairment had a higher mortality risk (HR = 2.31, 95% CI: 2.13, 2.51). Impairment in the subdomains of cognitive function were independently associated with elevated mortality risk in the participants with HI, with an HR ranging from 1.28 (copy figure) to 1.46 (speech and language).

Conclusions: Cognitive decline was common in individuals with HI, and those with HI and cognitive impairment further increased mortality risk. Our findings prompt a call for actions to improve the hearing status and cognitive function of older people to minimize health risks and improve longevity.

Keywords: hearing impairment, cognitive impairment, mortality, cohort study, aging

INTRODUCTION

Population aging represents the single most substantial demographic change of the 21st century, stemming from the decline in both fertility and mortality rates. The global number of people aged 60 years or older is projected to increase from 970 million to 2.1 billion in 2050 and 3.1 billion in 2100 (Ganesan et al., 2019). About 80% of the aging population will be in the developing countries (Ganesan et al., 2019). Population aging has resulted in a notable epidemiological transition, characterized by an increased prevalence of chronic diseases, including hearing impairment (HI) and cognitive impairment (Davis et al., 2016; Vancampfort et al., 2017; Ganesan et al., 2019).

The HI has become a common handicap across the globe (Brown et al., 2018) and as an age-related disease, HI imposes the burden on the society at large. A recent report by the *Annals of Internal Medicine* estimated that while two thirds of Americans aged 70 years or over have HI, only 15–20% of United States older adults use hearing aids, and disparities exist by ethnicity and socioeconomic status (Nieman and Oh, 2020). Similarly, in 2014–2015 a field survey in four representative provinces in China found that the prevalence rate of HI was approximately two thirds among Chinese adults aged 60 years or older (Gong et al., 2018). Etiologies of HI are multifactorial (Wang and Puel, 2020), involving genetic, chronic infectious, noise-induced, ototoxic (particularly iatrogenic ototoxicity), traumatic, immune-mediated, and age-related causes, among others. In addition, many people regard HI as a natural process of aging that can be ignorable. As a result, HI has not yet received enough attention it deserves. Previous studies reported that HI might be a modifiable condition and a possible target for secondary prevention of cognitive impairment in older age, dementia, social isolation, late-life depression, frailty and increased risk of mortality (Deal et al., 2017; Brenowitz et al., 2019; Wang and Puel, 2020). Further research is warranted to determine whether extensive hearing rehabilitative interventions could delay or halt cognitive decline and thereby lower the risk of mortality.

Cognitive impairment is among the most pressing public health concerns worldwide and has recently been found to be associated with HI (Lin and Albert, 2014; Martini et al., 2014; Loughrey et al., 2018; Powell et al., 2021). Previous studies exhibited that HI accelerated cognitive decline (Powell et al., 2021). However, the hearing decline is gradual and tends to go unrecognized, consequently, receives minimal attention (Michikawa et al., 2009). Gao et al. (2020), in their study of the CLHLS data sets of 2011/2012 and 2014 waves, confirmed that HI was negatively associated with cognitive function in older adults in China. The mechanism underlying the association between HI and cognitive impairment remains unclear, several postulations were proposed (e.g., information-degradation, sensory deprivation, and common pathologic etiology) (Lin and Albert, 2014; Martini et al., 2014; Loughrey et al., 2018; Powell et al., 2021). In addition, previous studies did not examine how HI, with or without cognitive impairment, impacts the all-cause mortality.

The relationship between HI and cognitive function and mortality is complex. Although the relationship between HI and mortality risk has been studied in the populations in high-income countries and the results were inconsistent (Genther et al., 2015; Engdahl et al., 2019; Lin et al., 2019; Miyawaki et al., 2020; Sun et al., 2020). However, the evidence from low- and middle-income countries are far from sufficient, because these countries are experiencing the fastest rise in life expectancy. In addition, a number of epidemiological studies have demonstrated an association between cognitive impairment and increased risk of mortality, with both mild and moderate-to-severe cognitive impairment being predictors of mortality in older people (Takata et al., 2014; An and Liu, 2016; Lv et al., 2019; Li et al., 2021). Nevertheless, previous studies on the association between HI and mortality did not examine the potential differences in the cognitive function and its subdomains in the older people, and further research is needed (Rabbitt, 1990; Baltes and Lindenberger, 1997; Dawes et al., 2015). Therefore, if HI and cognitive decline can serve as predictors of mortality, they should be studied to understand their impact on the mortality burdens.

In the present study, we used longitudinal cohort study data from the most recent 2011/2012 and 2014 CLHLS waves of follow-up to estimate (i) the association between time-varying HI and all-cause mortality among the oldest-old; (ii) the potential role of cognitive function and its subdomains in this relationship.

MATERIALS AND METHODS

Data Sources and Study Cohort

The present study took data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), which is an ongoing longitudinal study that began in 1998, along with seven follow-up surveys, with the new participants being added to replace the deceased who passed away in 2000, 2002, 2005, 2008, 2011/2012, 2014, and 2018 (Yang and Meng, 2020). The CLHLS recruited a representative sample from 23 of the 31 provinces of China and is the largest database on the oldest-old in the world, with the survey

Abbreviations: HI, hearing impairment; CLHLS, Chinese Longitudinal Healthy Longevity Survey; MMSE, Mini-Mental State Examination; CI, confidence interval; HR, hazard ratio; ADL, activities of daily living.

areas covering 85% of the Chinese population (Zeng, 2012). More details about the sampling procedure and quality of data of this survey have been published elsewhere (Zeng, 2012). Ethics approval was obtained from the Research Ethics Committees of Peking University (IRB00001052-13074). All participants or their legal representatives signed written consent forms in the baseline and follow-up surveys.

The CLHLS consisted of questions regarding self-reported hearing difficulties only in waves 2011/2012 and 2014. Thus, this study employed two waves from the CLHLS longitudinal data harvested during 2011/2012 to 2014. A total of 10,890 participants were enrolled, including 10,744 aged 65 years or older, with the latest follow-up conducted in 2018. Accordingly, 9,674 respondents were interviewed in 2011/2012 wave, and 1,070 newly enrolled respondents were interviewed in 2014 wave, respectively. Data were incomplete for 1,703 participants, and the amount of missing data (key variables) ranged from 54 to 1,005. The longest follow-up period lasted for up to 8 years, and 47.5% (n = 5,099) of the participants died during the follow-up period until 2018. Details of the sampling method and calculation of weights have been published previously (Dawes et al., 2015). Characteristics of the raw dataset were shown in **Supplementary Figure 1**.

Assessment of Hearing Status

Hearing sensations were assessed in terms of self-reported measures, and all enrolled participants were required to attend a series of standardized training sessions prior to interviews. Self-reported hearing status data were based on the responses to the question: "Do you have any difficulty with your hearing? "YES" was coded as having HI, while "No" signified not having HI (Gao et al., 2020)." A systematic review compared the results obtained with self-report to a hearing question with those obtained by pure tone audiometry. They found that older adults with HI can be recommended for an epidemiologic study if audiometric measurements cannot be performed (Valete-Rosalino and Rozenfeld, 2005). Therefore, self-reported hearing status is a suitable option for large epidemiological studies (Valete-Rosalino and Rozenfeld, 2005; Deepthi and Kasthuri, 2012; Diao et al., 2014).

Assessment of Cognitive Function

All participants were assessed for cognitive function by utilizing the Chinese version of the Mini-Mental State Exam (MMSE), a widely used cognitive test (Christensen et al., 2013). The test was tailored to the Chinese language based on the international standard of MMSE questionnaire, and had been proven to be reliable and valid in previous studies (Yi and Vaupel, 2010; Yuan et al., 2019; Duan et al., 2020; Zhang et al., 2021). The Chinese version of MMSE evaluates cognitive function in terms of 24 items, covering 7 sub-scales: orientation (4 points for time orientation and 1 point for place orientation); naming foods (naming as many kinds of food as possible in 1 min, 7 points); registration of 3 words (3 points); attention and calculation (mentally subtracting 3 iteratively from 20, 5 points); copy a figure (1 point); recall (delayed recall of the 3 words mentioned above, 3 points); and speech and language (2 points for naming objectives, 1 point for repeating a sentence, and 3 points for listening and following directions). The MMSE score ranges from 0 to 30. The higher the score, the better the cognitive function. The individuals who scored 25 or higher were considered to have normal cognitive function, and the summary accuracy at a cutoff value of 25 (10 studies) was sensitivity 0.87 and specificity 0.82 (Creavin et al., 2016). Cognitive impairment in this study was determined by its presence or absence according to this classification (Creavin et al., 2016).

Data on Mortality

Information on mortality was collected on the basis of death certificates provided by the local authorities. When such information was not available, relatives of the decedents were interviewed. Duration of follow-up was the time interval from the first interview date until the date of death. Participants who were alive at the last interview were regarded as being censored on the dates of their last interviews in 2018. The cause-specific mortality was not involved in this study because (1) a lot of the older adults died at home rather than in medical institutions where cause of mortality might be recorded, and (2) mortality surveillance systems are unsure in many survey fields (Duan et al., 2020).

Assessment of Potential Confounding Variables

A variety of variables were collected through a face-to-face interview against a standardized questionnaire, including sociodemographic features, lifestyles, health conditions and available medical services that were potentially associated with HI and cognitive impairment as suggested by previous studies (Dawes et al., 2015; Loughrey et al., 2018; Lv et al., 2019). Therefore, in this study, we assessed a range of these potential confounders by including the covariates age (continuous), gender (male or female), education background (no schooling or primary school or higher), occupation before retirement (manual or non-manual), ethnicity (Han or minority), residence (urban or rural), marital status (currently married and living with spouse, separated/divorced/never married, or widowed), tobacco smoking status (never or ever), alcohol drinking status (never or ever), regular leisure activities (yes or no), activity of daily living (ADL) (don't need help or need help), having been diagnosed with hypertension (yes or no), having been diagnosed with diabetes (yes or no), and baseline cognitive function (impaired or not impaired).

Statistical Analysis

First, we used multiple imputation to impute missing data for our raw dataset. The multiple imputation is based on chained equations and is commonly used for longitudinal studies. As multiple imputation uses information on baseline demographics and previous time points to predict missing values, the strategy assumes that data are missing at random, that is, that the missingness is related to observed data. We used some demographics such as gender, age, place of residence, as predictors, to impute the missing values of key variables.

We established 10 imputed datasets and carried out the pooled statistical inference.

For comparison, Chi-square test was used for categorical variables and the analysis of variance was employed for continuous variables. The Kaplan–Meier method was employed to plot the survival curves in terms of baseline hearing status and gender. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality by hearing status were calculated by using five dependent Cox proportional hazards models: Model 1: no variables adjusted; Model 2: additionally adjusted for gender, age, education background, residence, and marital status based on model 1; Model 3: additionally adjusted for smoking status, drinking status, regular leisure activities, and ADL based on model 2; Model 4: additionally adjusted for two kinds of diseases (hypertension and diabetes) based on model 3; and Model 5: additionally adjusted for baseline cognitive function based on model 4. Our test ascertained that the proportional hazard assumption was not been violated.

Next, in order to assess disparities across different populations, we conducted subgroup analyses in terms of baseline cognitive function (MMSE score ≥25 versus <25 points), age (65–79 versus ≥80 years), and gender (female versus male), respectively. In addition, we also examined whether the association of HI with mortality differed by baseline cognitive function and gender by separately adding an interaction term to the fully adjusted model. Moreover, we further examined the association of HI with all-cause mortality by seven cognitive subdomains among Chinese older adults.

In the end, to resolve the problem with the loss to follow-up, we performed a sensitivity analysis by removing incomplete cases. Additionally, we also conducted another sensitivity analysis by eliminating those who died within the half of the year after the baseline survey to account for the possibility that the pre-mortality dropped in hearing function and/or disease status could have influenced our results.

A two-tailed *p*-value of less than 0.05 was considered statistically significant. All analyses were performed by using R software package (version 4.1.1, the R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participant Characteristics

Table 1 presents the descriptive baseline characteristics in terms of different hearing states. A total of 10,744 enrolled participants aged 65 or older participated in the baseline survey in waves during 2011/2012 and 2014, and they were followed up for at least one wave. All participants were aged 86 years on average (range: 65–114 years) and more than half of them (55.5%) were female. Participants with HI more likely to be older, female, lower-educated, rural residents, widowed, separated, divorced or never married, no regular leisure activities, need help in ADL, having had hypertension and diabetes, and worse cognitive function. However, participants with HI were less likely to smoke and drink, but were more likely to have disease conditions (**Table 1**).

Kaplan–Meier Curves and Results of Multivariable Analysis in All Participants

Kaplan–Meier survival curve revealed a conspicuous probability of survival relationship between hearing status and all-cause mortality for total population (log-rank test for trend: $p < 0.001$) (**Figure 1**). The median survival time of none-HI and HI participants were 4.7 and 2.7 years, respectively, among the total population.

Table 2 shows the multivariable-adjusted HR and 95% CI of all-cause mortality by hearing status among Chinese older adults aged ≥65 years. The five multivariate models displayed consistent patterns between HI and all-cause mortality, and the association attenuated with more covariates included in the models. The unadjusted model (Model 1) showed that HI was significantly associated with the all-cause mortality. Compared to participants without HI, those who reported HI during the follow-up period were 2.29 times more likely to have all-cause mortality (95% CI: 2.16, 2.42). After adjustment for gender, age, education background, residence, and marital status in Model 2, the association between HI and mortality diminished significantly but remained comparable, with HR = 1.28 (95% CI: 1.20, 1.36). Model 3 (HR = 1.14, 95% CI: 1.07, 1.21) showed that HR decreased from 1.28 to 1.14 (i.e., 14% hazard ratio reduction) after adjustment for smoking, drinking, regular leisure activities, and ADL based on Model 2. Model 4 was additionally adjusted for two kinds of diseases (hypertension and diabetes) based on Model 3, and the results were consistent with Model 3. Model 5 was additionally adjusted for baseline cognitive function based on model 4, and the results suggested that HI was associated with a 7% [HR = 1.07, (95% CI: 1.00, 1.14)] increase in the risk of all-cause mortality compared with individuals without HI.

Subgroup Analyses

Figure 2 shows the HR of all-cause mortality by HI for different subgroups, conducted as separate models for each subgroup with full adjustment as in Model 5. The relationship and the effect sizes between HI and all-cause mortality were consistent across all subgroups in terms of cognitive function, age and gender. To examine whether the association between HI and all-cause mortality is modified by different cognitive states, we further tested the interaction between hearing status and cognitive function. The results showed that there was a significant interaction between HI and cognitive impairment ($p < 0.001$). HI participants with cognitive impairment showed higher mortality risk (HR = 2.31, 95% CI: 2.13, 2.51) than other groups (**Figure 3**). Similar associations were observed in the interaction analysis based on hearing status and gender. We also found that males had a higher risk of mortality (HR = 1.55, 95% CI: 1.37, 1.76) than their female counterparts, when they had the same level of HI (**Figure 3**).

Subdomain Analysis

We examined the seven cognitive subdomains separately for the association between HI and all-cause mortality.

TABLE 1 | Baseline characteristics by hearing status among Chinese aged ≥65 years.

	Hearing status[a]			
	None-HI	**HI**	**Total**	***P*-value[e]**
***N* (%)**	5665 (52.7)	5079 (47.3)	10744	
Age, years, median (25th, 75th)	81 (73, 89)	92 (84, 99)	86 (77, 95)	<0.001
Gender, count (%)				<0.001
Male	2724 (48.1)	2053 (40.4)	4777 (44.5)	
Female	2941 (51.9)	3026 (59.6)	5967 (55.5)	
Education attainment[b], count (%)				<0.001
No schooling	2881 (50.9)	3472 (68.4)	6353 (59.1)	
Primary school or higher	2784 (49.1)	1607 (31.6)	4391 (40.9)	
Main occupation before age 60, count (%)				<0.001
Non-manual	1016 (17.9)	617 (12.1)	1633 (15.2)	
Manual	4649 (82.1)	4462 (87.9)	9111 (84.8)	
Ethnicity, count (%)				0.261
Han	5237 (92.4)	4791 (94.3)	10028 (93.3)	
Others (minority)	428 (7.6)	288 (5.7)	716 (6.7)	
Residence, count (%)				0.001
Urban	2611 (46.1)	2285 (45.0)	4896 (45.6)	
Rural	3054 (53.9)	2794 (55.0)	5848 (54.4)	
Marital status, count (%)				<0.001
Currently married and living with spouse	2616 (46.2)	1216 (23.9)	3832 (35.7)	
Others[c]	3049 (53.8)	3863 (76.1)	6912 (64.3)	
Tobacco smoking status, count (%)				<0.001
Never	3689 (65.1)	3564 (70.2)	7253 (67.5)	
Ever	1976 (34.9)	1515 (29.8)	3491 (32.5)	
Alcohol drinking status, count (%)				0.001
Never	3903 (68.9)	3647 (71.8)	7550 (70.3)	
Ever	1762 (31.1)	1432 (28.2)	3194 (29.7)	
Regular leisure activities, count (%)				<0.001
Yes	3444 (60.8)	1679 (33.1)	5123 (47.7)	
No	2221 (39.2)	3400 (66.9)	5621 (52.3)	
ADL, count (%)				<0.001
Don't need help	4752 (83.9)	3115 (61.3)	7867 (73.2)	
Need help	913 (16.1)	1964 (38.7)	2877 (26.8)	
Self-reported hypertension, count (%)				<0.001
With	1803 (31.8)	1399 (27.5)	3202 (29.8)	
Without	3862 (68.2)	3680 (72.5)	7542 (70.2)	
Self-reported diabetes, count (%)				0.001
With	288 (5.1)	192 (3.8)	480 (4.5)	
Without	5377 (94.9)	4887 (96.2)	10264 (95.5)	
Cognitive function[d], count (%)				<0.001
Impaired	1412 (24.9)	3081 (60.7)	4493 (41.8)	
Not impaired	4253 (75.1)	1998 (39.3)	6251 (58.2)	

HI, hearing impairment; ADL, activities of daily living.
[a]Hearing status was defined by responses of self-reported hearing status: none-HI and HI.
[b]Education background was defined by education attainment. None: school years = 0; primary school: school years = 1–5; middle school or higher: school years > 5.
[c]'Others' include widowed, separated, divorced and never married.
[d]Cognitive function was classified into two mutually exclusive groups: not impaired (25 ≤ MMSE score ≤ 30), and impaired (0 ≤ MMSE score ≤ 24).
[e]Chi-square test was used for categorical variables, and analysis of variance was used for continuous variables.

Impairment in orientation, naming foods, registration, attention and calculation, copy figure, delayed recall, and speech and language was independently associated with elevated mortality risk in the participants with HD, with HR ranging from 1.28 (copy figure) to 1.46 (speech and language) (**Table 3**).

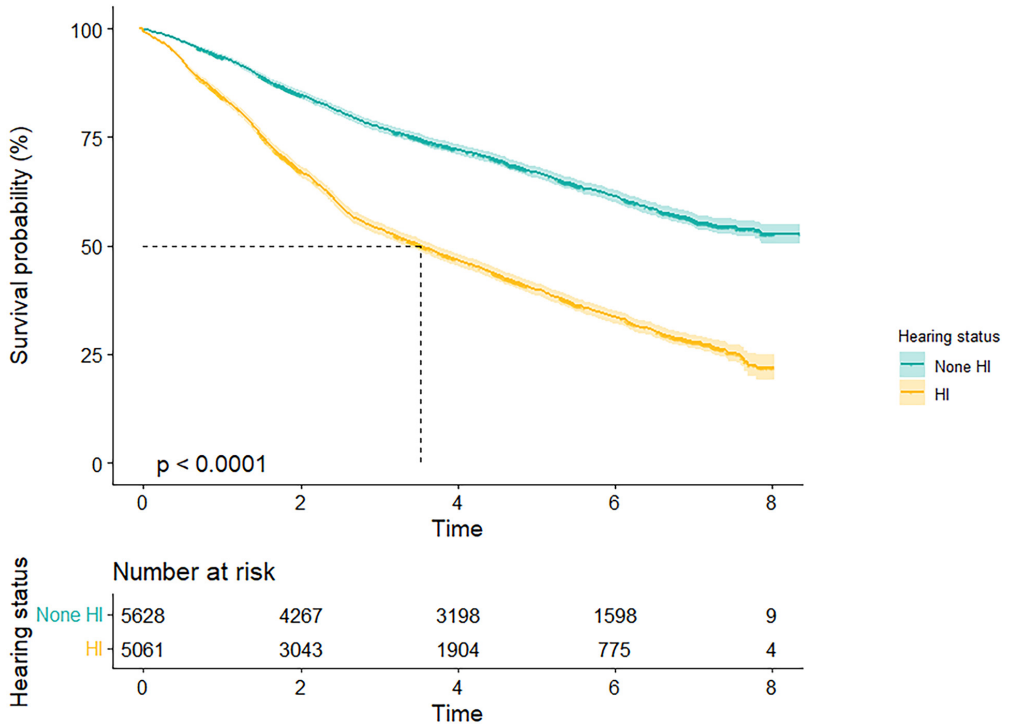

FIGURE 1 | Survival probability by different hearing states. Kaplan–Meier survival curves illustrated a conspicuous probability of survival relationship between hearing status and all-cause mortality for total population ($p < 0.001$). HI, hearing impairment.

Sensitivity Analysis

Among the cohorts, there was almost no change in the association between HI and all-cause mortality after excluding participants lost to follow-up or with survival time less than half of the year. The association was still robust after further adjustment for potential confounders (**Supplementary Tables 1, 2**).

DISCUSSION

With the population aging, an increasing number of people are living with HI, especially during their later-life years, which can bring about multiple health problems. To our knowledge, this is the first longitudinal survey to examine if HI bears a relation with all-cause mortality and what role the cognitive function plays in Chinese adults aged 65 years or older. Subgroup and sensitivity analyses revealed that the associations remained robust.

Findings of the present study suggested that the prevalence of HI was 47.3% (59.6% women), with gender being highly correlated with HI. The incidence of HI in our cohort was similar to that in the United States and Western European countries (Roth et al., 2011; Tyagi et al., 2021). The Framingham Cohort Study (n = 1,672, mean age = 59 years, 57.6% women) (Tyagi et al., 2021) found that the prevalence of abnormal hearing patterns stood at 57.3% (i.e., 20.3% cochlear-conductive; 20.3% sensorineural; 7.7% low-sloping; and 8.0% strial). A review concluded that approximately 30% of men and 20% of women in Europe have a hearing loss of 30 dB or more by the age 70 years, and 55% of men and 45% of women by the age 80 years (Roth et al., 2011). Additionally, in line with previous studies (Feeny et al., 2012; Denney and Boardman, 2021), we found that the aging male participants with HI carried a higher risk of mortality than their female counterparts after adjusting for confounding factors. The gender differences might be ascribed to the following reasons: (i) males had a higher innate and pro-inflammatory activity and lower adaptive immunity (i.e., testosterone has an immunosuppressive effect while estrogen has an immunoenhancing effect on the immune system) (Taneja, 2018); (ii) males had a higher incidence of smoking and drinking in the CLHLS dataset, and these risk factors act as drivers for mortality risk, leading to the differences (Feeny et al., 2012). The finding reminds us that when the government and organizations are building programs to prevent hearing function, gender differences should not be ignored.

Consistent with previous studies (Takata et al., 2014; Lv et al., 2019; Li et al., 2021), our study, using the CLHLS database, yielded an important finding that self-perceived HI is associated with the risk for all-cause mortality independent of demographics, health behaviors, certain comorbidities, and baseline cognitive function. In a nationally representative dataset in United States, involving 215.6 million Americans (mean age = 45.9 years, 51.7% female), Lin et al. (2019) revealed a 5-year mortality rate of 3.0% in those with good hearing and a rate of 19.5% in participants with HI and a rate of 17.8% in deaf individuals. Genther et al. (2015) analyzed audiologic data from 1,958 adults aged 70–79 years from the Health,

TABLE 2 | Multivariable-adjusted hazard ratios and 95% confidence intervals of all-cause mortality by hearing status.

Model	Model 1	Model 2	Model 3	Model 4	Model 5
	Hazard ratio (95% CI)				
Hearing impairment					
No	–	–	–	–	–
Yes	2.29 (2.16, 2.42)	1.28 (1.20, 1.36)	1.14 (1.07, 1.21)	1.14 (1.07, 1.21)	1.07 (1.00, 1.14)
Gender					
Female	–	–	–	–	–
Male		1.42 (1.33, 1.52)	1.43 (1.33, 1.54)	1.43 (1.33, 1.54)	1.46 (1.35, 1.57)
Age	–	1.07 (1.07, 1.08)	1.05 (1.05, 1.06)	1.05 (1.05, 1.06)	1.05 (1.05, 1.06)
Education attainment					
Primary school or higher	–	–	–	–	–
None		1.14 (1.06, 1.22)	1.08 (1.01, 1.16)	1.08 (1.01, 1.16)	1.04 (0.97, 1.12)
Residence					
Rural	–	–	–	–	–
Urban		1.04 (0.99, 1.10)	1.07 (1.01, 1.13)	1.07 (1.01, 1.13)	1.05 (0.99, 1.11)
Marital status					
Currently married and living with spouse	–	–	–	–	–
Others[a]		1.25 (1.16, 1.35)	1.19 (1.10, 1.28)	1.19 (1.10, 1.29)	1.17 (1.08, 1.26)
Smoke status					
Never	–	–	–	–	–
Ever			1.11 (1.03,1.19)	1.10 (1.03,1.19)	1.13 (1.05, 1.21)
Drink status					
Never	–	–	–	–	–
Ever			1.01 (0.95, 1.08)	1.01 (0.95, 1.08)	1.01 (0.94, 1.08)
Regular leisure activities					
Yes	–	–	–	–	–
No			1.78 (1.66, 1.90)	1.77 (1.65, 1.90)	1.65 (1.54, 1.77)
ADL					
Don't need help	–	–	–	–	–
Need help			1.71 (1.61, 1.82)	1.71 (1.60, 1.82)	1.60 (1.50, 1.70)
Self-reported hypertension					
Without	–	–	–	–	–
With				0.98 (0.92, 1.04)	0.98 (0.92, 1.04)
Self-reported diabetes					
Without	–	–	–	–	–
With				1.34 (1.17, 1.54)	1.33 (1.16, 1.53)
Cognitive function					
Not impaired	–	–	–	–	–
Impaired					1.47 (1.38, 1.58)

CI, confidence interval; ADL, activities of daily living.
Model 1: No variables adjusted.
Model 2: Additionally adjusted for gender, age, education attainment, residence, and marital status based on model 1.
Model 3: Additionally adjusted for smoking status, drinking status, regular leisure activities, and ADL based on model 2.
Model 4: Additionally adjusted for two kinds of diseases (hypertension and diabetes) based on model 3.
Model 5: Additionally adjusted for cognitive function based on model 4.
[a] *'Others' include widowed, separated, divorced and never married.*

Aging, and Body Composition Study. They found a HR of 1.64 for mortality in individuals with HI, as compared to normal hearing individuals, and the association remained consistent (HR = 1.20, 95% CI: 1.03–1.41) when the effects were adjusted for demographics and cardiovascular risk factors. Our results demonstrating attenuation of the association of HI and mortality after adjustment for demographics and cardiovascular factors are consistent with these previous findings.

Our study revealed that poor cognitive performance was common in individuals with HI, and its interaction with cognitive impairment further increased mortality risk in older adults. Additionally, we also found that impairment in the subdomains of cognitive function was independently associated with increased mortality risk among participants with HI, especially in the subdomains of speech and language. Multiple assumptions have been put forward to explain

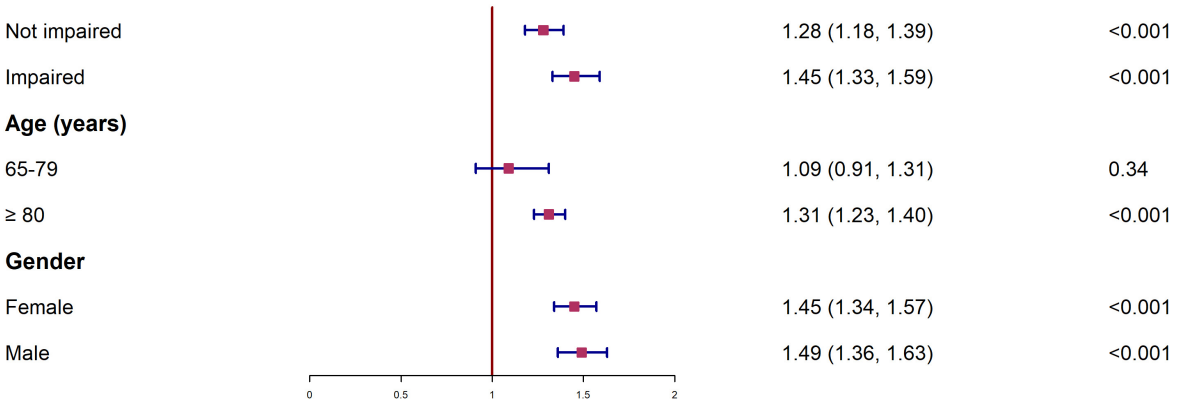

FIGURE 2 | Multivariable-adjusted hazard ratios and 95% confidence intervals of all-cause mortality for different subgroups. †All models were adjusted for gender, age education, residence, and marital status, smoking status, drinking status, regular leisure activities, ADL, hypertension and diabetes. HI, hearing impairment; HR, hazard ratio; CI, confidence interval; ADL, activities of daily living.

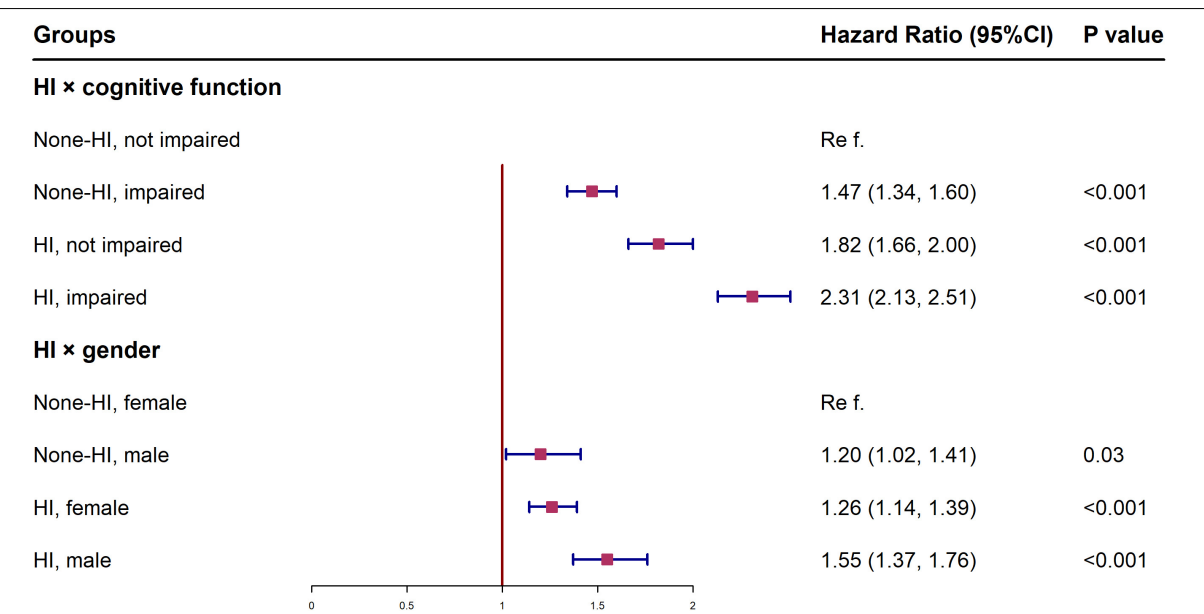

FIGURE 3 | Interactions between hearing status and cognitive function, gender in the association with all-cause mortality among Chinese aged ≥65 years. †All models were adjusted for gender, age, education, residence, and marital status, smoking status, drinking status, regular leisure activities, ADL, hypertension and diabetes. HI, hearing impairment; CI, confidence interval; ADL, activities of daily living.

the association between HI and cognitive impairment (Lin and Albert, 2014; Yamada et al., 2016; Powell et al., 2021). The first is the information-degradation hypothesis, which postulates that the increased cognitive load associated with HI adjustment may deplete available resources for performing other cognitive activities. The second is the sensory deprivation hypothesis: that is, HI leads to cortical re-allocation, deafferentation, or atrophy to support speech perception processing. The third hypothesis is a shared pathologic etiology: i.e., a common cause such as aging or microvascular disease may result in both HI and cognitive impairment. Based on the hypothesis model of HI and cognitive function proposed by Lin and Albert (2014), we further put forward a possible mechanism by which HI and cognitive impairment work on all-cause mortality (**Supplementary Figure 2**). Specifically, HI in the presence of cognitive impairment may serve as a marker for frailty (e.g., physical, cognitive, social, and psychological frailty) (Fried et al., 2001; Panza et al., 2018), which is a powerful predictor of mortality.

TABLE 3 | Association of hearing impairment with all-cause mortality by different cognitive function subdomains[a].

Subdomains[b]	Hazard ratio (95% CI)	*P*-value
Orientation		<0.001
Not impaired	–	
Impaired	1.43 (1.34, 1.52)	
Naming foods		<0.001
Not impaired	–	
Impaired	1.31 (1.23, 1.39)	
Registration		<0.001
Not impaired	–	
Impaired	1.37 (1.29, 1.46)	
Attention and calculation		<0.001
Not impaired	–	
Impaired	1.32 (1.24, 1.40)	
Copy figure		<0.001
Not impaired	–	
Impaired	1.28 (1.18, 1.39)	
Delayed recall		<0.001
Not impaired	–	
Impaired	1.35 (1.27, 1.43)	
Speech and language		<0.001
Not impaired	–	
Impaired	1.46 (1.36, 1.55)	

HI, hearing impairment; CI, confidence interval; MMSE, mini-mental state examination; ADL, activities of daily living.
[a]Measured by the MMSE, and each of the seven cognitive subdomains was dichotomized with full score indicating no impairment and all others as impaired.
[b]Each model was adjusted for all the covariates, including demographics (gender, age, education, residence, and marital status), and smoking status, drinking status, regular leisure activities, ADL, hypertension and diabetes.

Our study has its own strengths and limitations. On the one hand, the power of this study lies in that it was a large nationally-representative cohort of the oldest-old population, with negligible loss to follow-up in terms of mortality. In addition, the protracted follow-up period enabled us to conduct in-depth subgroup and subdomain analyses upon adjustment for potential confounding variables. On the other hand, hearing sensations were assessed in terms of self-reported measures, which did not reflect the severity of HI. Audiometry is the gold standard for evaluation of hearing loss, but large-scale use of the procedure involves operational difficulties (Deepthi and Kasthuri, 2012; Diao et al., 2014). Additionally, our cognitive function depended on the MMSE. Albeit it has been validated in population-based studies, it is not a professional diagnosis of cognitive impairment (Christensen et al., 2013; Creavin et al., 2016). Finally, we did not have access to detailed information about the specific cause and duration of HI. Further studies are warranted to examine the relationship between HI and mortality in varied degrees and durations.

CONCLUSION

The data from this population-based longitudinal study revealed a conspicuous probability of survival relationship between hearing status and all-cause mortality in Chinese aged 65 or older. The association remained robust in subgroup and sensitivity analyses. In addition, cognitive decline was common in individuals with HI, and its interaction with cognitive impairment further increased mortality risk in older adults. Our findings prompt a call for actions to improve the hearing status and cognitive function of older people to minimize health risks and improve longevity.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committees of Peking University (IRB00001052-13074). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-LZ and W-JK designed the research and directed its implication. JW, DL, and ET prepared and analyzed the data and drafted the manuscript. Z-QG and J-YC contributed to the data management. All co-authors contributed to the manuscript's modifications and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.865821/full#supplementary-material

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ORIGINAL RESEARCH
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Using Auditory Characteristics to Select Hearing Aid Compression Speeds for Presbycusic Patients

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Objectives: This study aimed to select the optimal hearing aid compression speeds (fast-acting and slow-acting) for presbycusic patients by using auditory characteristics including temporal modulation and speech-in-noise performance.

Methods: In total, 24 patients with unilateral or bilateral moderate sensorineural hearing loss who scored higher than 21 on the Montreal Cognitive Assessment (MoCA) test participated in this study. The electrocochleogram (ECochG) results, including summating potentials (SP) and action potentials (AP), were recorded. Subjects' temporal modulation thresholds and speech recognition at 4 individualized signal-to-noise ratios were measured under three conditions, namely, unaided, aided with fast-acting compression (FAC), and aided with slow-acting compression (SAC).

Results: The results of this study showed that modulation discrimination thresholds in the unaided (−8.14 dB) and aided SAC (−8.19 dB) conditions were better than the modulation thresholds in the FAC (−4.67 dB) conditions. The speech recognition threshold (SRT75%) for FAC (5.21 dB) did not differ significantly from SAC (3.39 dB) ($p = 0.12$). A decision tree analysis showed that the inclusion of the AP, unaided modulation thresholds, and unaided SRT75% may correctly identify the optimal compression speeds (FAC vs. SAC) for individual presbycusic patients with up to 90% accuracy.

Conclusion: Both modes of compression speeds improved a presbycusic patient's speech recognition ability in noise. The SAC hearing aids may better preserve the modulation thresholds than the FAC hearing aids. The measurement of AP, along with the unaided modulation thresholds and unaided SRT75%, may help guide the selection of optimal compression speeds for individual presbycusic patients.

Keywords: presbycusis, hearing aid, temporal modulation, speech recognition in noise, decision tree

INTRODUCTION

Hearing affects people's quality of life. Presbycusis, or age-related hearing loss (ARHL), is a degenerative change of the auditory system associated with aging, often accompanied by decreased speech recognition of noise (Gates and Mills, 2005; Liu and Yan, 2007). Presbycusis not only affects daily communication and independent living but also increases the risk of cognitive decline resulting in dementia (Fortunato et al., 2016; Su et al., 2017; Bowl and Dawson, 2019). At present, hearing aids and cochlear implants are the only intervention measures to improve the hearing ability of elderly hearing-impaired patients (Sprinzl and Riechelmann, 2010). However, due to individual differences, hearing aids may not always provide the most optimal speech intelligibility for all individual patients. A strategy that considers individual characteristics in the selection of optimal hearing aid may be beneficial.

A major complaint from presbycusic patients is poor speech understanding in noise (speech in noise or SIN). Previous studies proposed that the reduced temporal processing ability of the elderly hearing-impaired listeners may account for some of the difficulties (Abel and Hay, 1996; Phillips, 1999; Wingfield et al., 2006; Anderson et al., 2012; Sergeyenko et al., 2013; Bramhall et al., 2015; Rance and Starr, 2015; Han and Dimitrijevic, 2020; Lad et al., 2020; Luo and Ding, 2020; Shader et al., 2020). Temporal resolution refers to the ability of the auditory system to respond to rapid changes in the acoustic signal. Temporal information can be divided into a temporal fine structure (TFS), periodicity, and temporal envelope (ENV). Several studies showed that the reserve of ENV can keep the sound naturalness, and TFS may be related to melody, tonal perception, and speech recognition in noise (Moon and Hong, 2014).

The inner hair cells of the cochlea are connected with the auditory nerve fibers through ribbon synapses. In mammals, auditory nerve fibers can be broadly divided into two types based on spontaneous discharge rate (SR), namely, low SR fibers and high SR fibers, which accounted for 40 and 60% of the total nerve fibers, respectively (Mohrle et al., 2016). High SR fibers have a lower threshold and play a leading role when sound intensity approaches the behavioral auditory threshold, and their discharge rate saturates at 20–30 dB above the threshold. However, low SR fibers have a higher threshold and a wider dynamic range and are helpful for sound recognition in noise (Profant et al., 2019). Animal studies have shown that noise exposure and aging lead to the loss of acoustic nerve fibers, especially low SR fibers, without significant threshold shifts (Frisina and Frisina, 1997). Animal experiments and computer simulation results suggest that the loss of low SR fibers affects the time coding of the sound envelope at suprathreshold levels (Grose and Hall, 2006). A study by Otte et al. (1978) showed that humans lose about 2,100 auditory neurons every 10 years. Studies found that the retainment of only 10–20% of the inner hair cells can keep a normal audiometric threshold, but a smaller percentage of fiber loss can lead to the decline of speech recognition ability (Lobarinas et al., 2013). Thus, listeners with degraded temporal resolution will have difficulty in speech recognition in challenging environments, even if they do not have hearing loss or difficulty in quiet environments (Grose and Mamo, 2010; Jayakody et al., 2018). Temporal resolution decreases with age (Queiroz et al., 2010; Lister et al., 2011; Fostick and Babkoff, 2013; Ozmeral et al., 2016). Thus, the elderly listeners will have difficulty with tasks such as temporal modulation discrimination, which measures a listener's ability to distinguish how much fluctuation in the intensity of a signal (or modulation depth) can be discriminated (Herrmann et al., 2019; Luo et al., 2020; Zhou et al., 2020; Mepani et al., 2021).

Bharadwaj et al. reported that in animal experiments, the loss of lower SR fibers led to a reduction in the supra-threshold amplitude of the ABR I wave (Bharadwaj et al., 2014; Mohrle et al., 2016). Other studies also showed that the amplitude of ABR wave I and action potential (AP) were sensitive measurements in potential noise-induced cochlear synapse disease (Liberman et al., 2016; Mehraei et al., 2016; Lobarinas et al., 2017; Valderrama et al., 2018). AP represents the total activity of auditory nerve fibers connected with hair cells, and the first negative wave of AP is defined as N1, which is the same component as ABR wave I and originates from the distal portion of the auditory nerve (Moller and Jannetta, 1983). Studies suggested that cochlear synaptopathy influences the connection between inner hair cells (IHC) and auditory nerves, resulting in low SR fiber dysfunction and thus reducing speech perception in noise (Furman et al., 2013). Chen et al. (2021) studied the effect of cochlear synaptopathy on presbycusis using ECochG; they found that some presbycusic patients may have cochlear synaptopathy, manifested by lower AP amplitude, causing speech perception in noise dysfunction. Since in sensorineural hearing loss, the ABR wave I often disappear, AP may be a viable measure to reflect the condition of the low SR fibers and cochlear synapses.

Souza reported that the temporal resolution of the individual listeners could affect their speech recognition (Souza, 2000). As hearing aids could alter the temporal and spectral characteristics of the input signals reaching the listener's auditory system, it is reasonable to expect that the type of compression processing in a hearing aid could affect the aided temporal resolution and/or aided speech in noise ability. Today's hearing aid compression patterns can be broadly classified into fast-acting compression (FAC) and slow-acting compression (SAC) types. Fast-acting compression hearing aids typically have attack times under 10 ms and release times between 5 and 200 ms (Kuk and Hau, 2017). They are also called syllabic compressors because the gain change in such devices follows the rapid intensity level changes between syllables of speech. A rationale for FAC is to ensure audibility and that the output sound intensity is within the residual hearing range of the hearing-impaired listeners. In so doing, FAC reduces the intensity contrasts between the louder and softer parts of the input signals (i.e., reduces modulation or increases smearing). SAC hearing aids typically use longer attack times (5–100 ms) and release times (as long as 2 s, but in some hearing aids, it can be as long as 20 s). This longer time constant maintains the intensity contrasts of the input signal (i.e., less smearing). On the contrary, the longer release time in the SAC may not provide sufficient gain to softer sounds following a more intense sound and loss of audibility may ensue.

There have been numerous experimental studies on the effect of FAC and SAC hearing aids. The majority of the studies reported that the sound quality of SAC hearing aids is generally preferred over FAC hearing aids (Korhonen et al., 2021). The results are mixed when speech recognition was considered. Some researchers believed that FAC can retain TFS better than SAC during the dip period of background noise. This helps the listeners to extract the target speech information (Festen and Plomp, 1990; Vestergaard et al., 2011; Kwon et al., 2012; Ozmeral et al., 2012). For example, Gatehouse et al.'s study on ten normal-hearing native-English speaking listeners found that the optimal compression speed varies from individual to individual, but most people get better speech recognition in noise with FAC than SAC (Gatehouse et al., 2006a,b). Moore et al. studied the relative benefits of SAC and FAC in 2-talker babble noise. When the direction of the speech signal and noise signal was different, the speech recognition ability of SAC was slightly better than that of FAC (Moore et al., 2010). Reinhart and Souza also found that for a high compression ratio, SAC resulted in better speech recognition (Reinhart and Souza, 2016). These conflicting results may be due to differences in materials, parameters of compression, and outcome measures used in different studies, and partly caused by individual differences among listeners. Souza reported that temporal resolution will influence speech recognition (Souza, 2000), and SAC can preserve the temporal waveform better than FAC (Kuk and Hau, 2017). So, we inferred that unaided temporal resolution may influence the outcome of the comparison between compression speeds. If the listeners have a good unaided temporal resolution, to begin with, they may not be as negatively affected by FAC (from the smearing); thus, no difference between FAC and SAC may result. If listeners have a poor unaided temporal resolution, they may be more negatively affected by FAC and less by SAC. Therefore, we suggest that measuring the unaided temporal resolution and the unaided speech in noise ability of the individual may offer insight into whether the patient may benefit more from FAC or SAC.

In this study, we plan to evaluate the effect of FAC and SAC on presbycusic patients' temporal modulation discrimination thresholds and speech in noise ability. These threshold measures will be combined with other individual audiometric characteristics in a decision tree analysis in order to help to preselect the optimal compression speed for better-aided speech recognition in noise.

METHODS

Participants

The current dataset was based on 24 patients (9 male patients and 15 female patients, average age = 77 years) who were treated at Peking University First Hospital for hearing problems between March 2019 and June 2021. All patients have signed informed consent. Mandarin was their native language. Patients completed their medical case history intake and standard audiometry [including pure tone audiometry (PTA) and speech audiometry; electrocochleogram was also measured]. The Montreal Cognitive Assessment (MoCA) was also administered to rule out significant cognitive impairment.

The demographic details and audiometry results are shown in **Table 1**. Audiometric thresholds of subjects' tested ears are shown in **Figure 1**.

Selection and Fitting of Test Hearing Aids

Two hearing aids with different modes of compression speeds were compared. The first was a 15-channel hearing aid that primarily uses SAC. It uses an adaptive attack time of <2 s and a release time of <20 s. The second was a 16-channel hearing aid that was used in the "syllabic compression" mode during this study (typically an attack time of <5 ms and a release time of <50 ms). Other than the compression algorithm, all other features within the hearing aids were deactivated during the study. Both hearing aids were fitted to the NAL-NL2 target by the same experimenter and verified using real-ear measurement to ensure that the target output between the two hearing aids was matched to within 3 dB at 500–4,000 Hz.

Because subjects were patients seeking hearing treatment, and binaural hearing aids, despite the clinicians' recommendations, were not a common practice in China, subjects were fitted and studied monaurally in the ear with a moderate-to-severe hearing loss. If both ears had moderate-to-severe sensorineural hearing loss, the test ear was randomly selected. The order of hearing aids tested was randomized. Subjects were blinded to the test hearing aids.

Test and Stimulus Conditions

Temporal resolution was measured using a temporal modulation discrimination test written by the School of Electronics Engineering and Computer Science at Peking University. The test

TABLE 1 | Demographic details and audiometry results of 24 subjects.

Age (year), median (Q1, Q3)	75.7, 77 (73.5, 81)
Male, *n* (%)	9 (37.5)
PTA (dB HL), median (Q1, Q3)	52.6, 51.7 (50.8, 55)
MoCA (point), median (Q1, Q3)	24.5, 25.5 (22.5, 27)
ECochG (-SP/AP %), median (Q1, Q3)	39.8, 38.5 (24.5, 57)
AP, median (Q1, Q3)	0.756, 0.745 (0.415, 1.023)

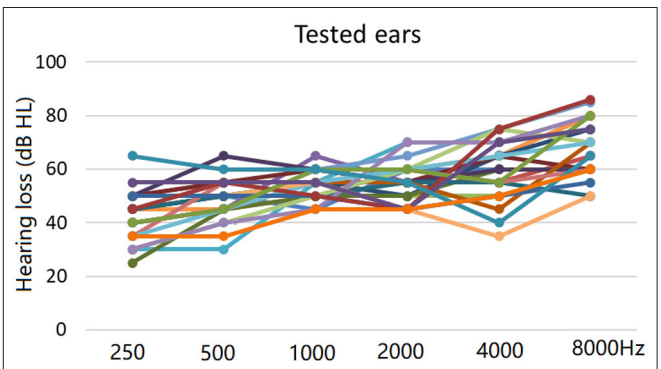

FIGURE 1 | Individual audiometric thresholds in test ears (13 left ears and 11 right ears) using pure tone audiometry.

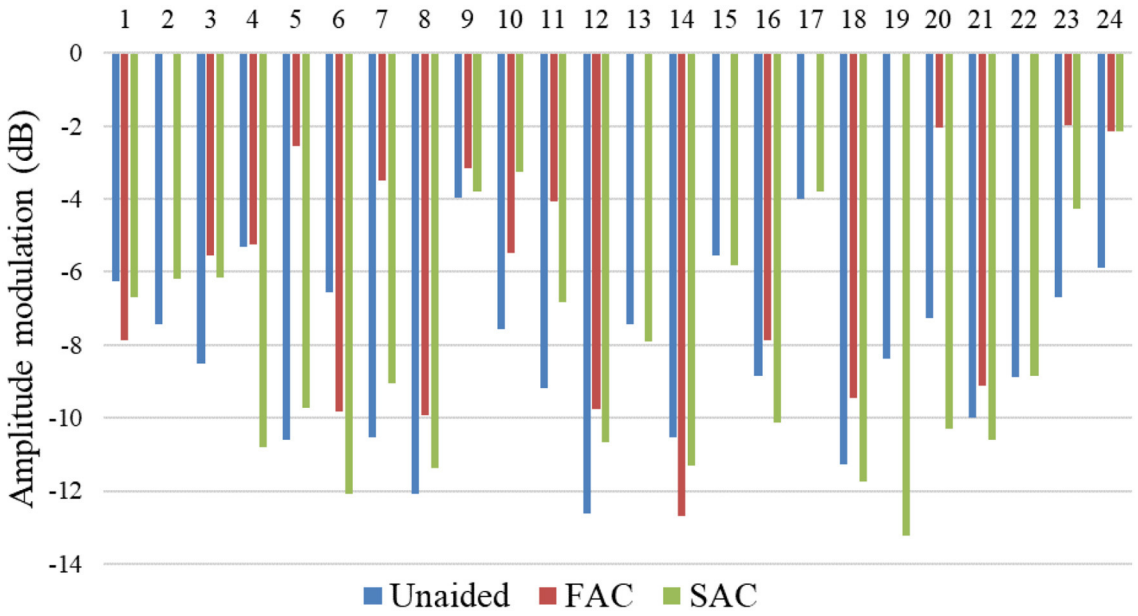

FIGURE 2 | Temporal modulation discrimination thresholds measured across participants.

stimuli were cosine modulated sinusoids with a carrier frequency at 1 kHz and a duration of 600 ms. The default modulation rate for the amplitude modulation was 4 Hz. The standard stimuli were modulated at a modulation depth of −15 dB. The target modulation depth was initially set to −3 dB and adaptively varied in 2 dB and then 1 dB steps using a two-down one-up rule. The RMS level of the standard and target stimuli was normalized and roved at ±2 dB. A three alternative forced choice (3AFC) paradigm was used in which subjects selected the interval that sounded different. A modulation threshold of "0" would suggest 100% modulation or poor temporal resolution, whereas a more negative modulation threshold (e.g., −30 dB) would suggest a better temporal resolution. The unaided modulation threshold was measured at 85 dB SPL, while the aided thresholds were measured at a stimulus level of 80 dB SPL.

Speech recognition in noise was evaluated using the computer-aided Chinese speech audiometry platform (Ji et al., 2011a,b; Xi et al., 2012). Subjects identified the target sentence in 4-talker babble noise. Four customized signal-to-noise ratio (SNR) conditions (ranging from −12 dB to 18 dB) were used to obtain as broad a representation of the individual performance-intensity (P-I) function as possible in each test condition. That is, we attempted to test SNRs that yielded ≥50% speech recognition and that yielded <50% speech recognition. The target speech (sentence) and background (4-talker) were presented directly in front of the subject at a speech level of 85 dB SPL in the unaided mode and 80 dB SPL in the aided mode.

Procedures

The medical case history intake and standard audiometry (including PTA and speech audiometry) were first performed along with ECochG. MoCA was administered to ensure no significant cognitive impairment. The two test hearing aids were then fitted before their amplitude modulation discrimination thresholds and speech-in-noise performance was measured under three conditions, namely, unaided, aided with FAC, and aided with SAC, in random order. Patients are blinded to the identity of the hearing aids. After the initial decision tree analysis, another 10 listeners (see later) were enrolled to verify the accuracy of the decision tree prediction.

Testing on speech recognition, amplitude modulation was conducted in a soundproof room with the stimuli presented directly in front of the subject by a soundbox. Stimuli intensity was measured by a sound pressure meter at 85 dB SPL during the unaided condition and 80 dB SPL in the aided condition with FAC and SAC (OTO suite was used as the test computer system). Subjects were tested monaurally with the non-test ear occluded with an earplug (made by OHRFRIEDEN with attenuation factor < 32 dB). Amplitude modulation discrimination thresholds were determined first, followed by a 10-min break before the speech in noise measurement was conducted. During each test, subjects were tested in the unaided, aided with FAC, and aided with SAC conditions in random order.

Statistical Analysis

All the data were normally distributed, and standard independent *t*-tests were conducted. Python3.8 is used for statistical analysis based on sklearn and stats models. $P < 0.05$ is considered to be statistically significant.

Ethics Statement

All protocols for this study were conformed to the Declaration of Helsinki and approved by the Biomedical Research Committee of the Peking University First Hospital (2020-219). The

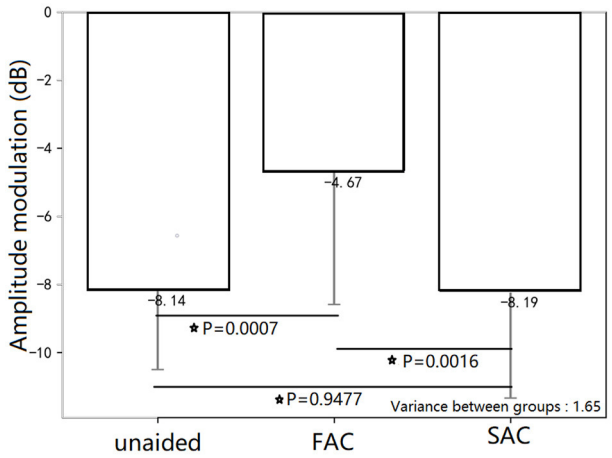

FIGURE 3 | Mean temporal modulation discrimination thresholds for the three HA conditions. The unaided temporal modulation thresholds and the aided temporal modulation thresholds in the SAC condition were better than that in the aided FAC condition. There was no significant difference in temporal modulation thresholds between unaided and aided SAC conditions. The * symbol means statistically significant.

patients/participants provided their written informed consent to participate in this study.

RESULTS

Temporal Amplitude Modulation Thresholds

The individual temporal modulation thresholds are summarized in **Figure 2**. The mean unaided modulation threshold was −8.14 dB. The mean aided modulation threshold using FAC was −4.67 dB and that for SAC was −8.19 dB. As a reminder, a smaller modulation threshold reflects better temporal resolution.

The mean unaided and aided modulation thresholds were reported in **Figure 3**. An independent *t*-test showed that the unaided modulation threshold and the aided modulation thresholds measured in the SAC were better than that using FAC. There was no significant difference in modulation thresholds between the unaided and aided SAC conditions. Thus, the acoustic changes resulting from different compression speeds can influence an individual's measured temporal resolution.

Speech in Noise Performance

Logistic functions were fitted to each individual subject's data at the 4 individualized SNRs for each test condition. In generating the logistic functions, we assigned a performance of 0% when the SNR was −10 dB and 100% when the SNR was 30 dB. The generated logistic functions, which represent the subjects' performance across a range of SNRs for each hearing aid condition (unaided, FAC, SAC), are summarized in **Figures 4A–C**.

Using this function, we estimated the speech reception threshold (SRT) at a criterion level of 75% (SRT75%) to reflect more closely on the SNR condition that subjects needed for

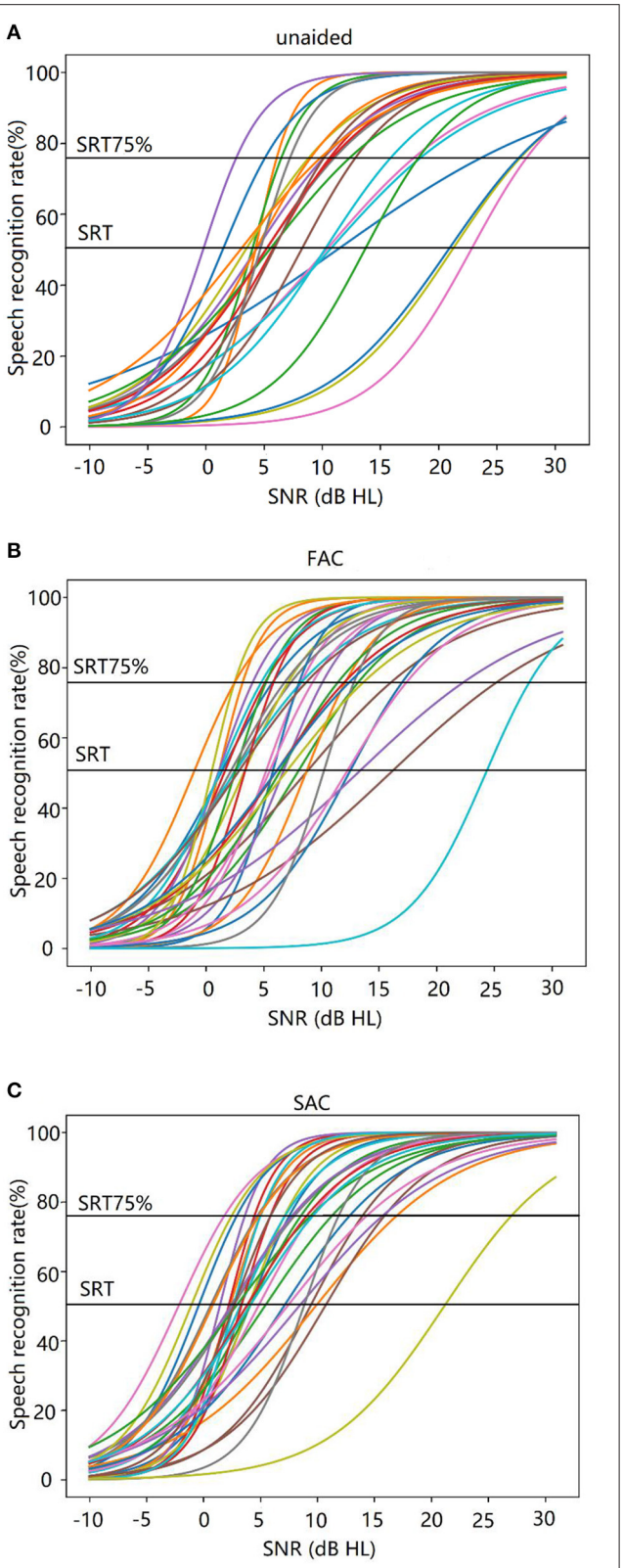

FIGURE 4 | (A–C) Individual logistic functions (or performance-intensity functions) estimated across signal-to-noise ratios. **(A)** Unaided, **(B)** FAC, and **(C)** SAC.

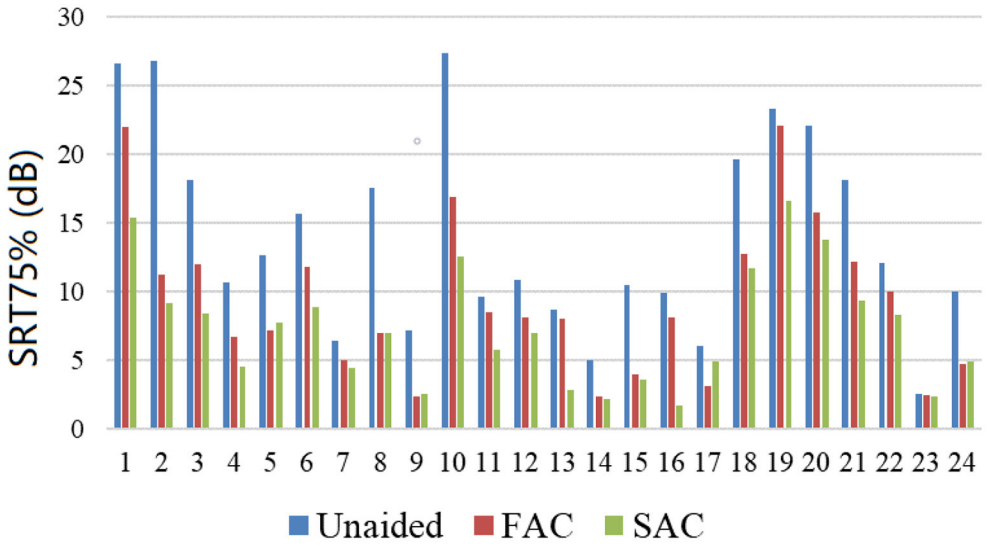

FIGURE 5 | SRT75% measured across participants.

successful daily communication in real life (Smeds et al., 2015; Wu et al., 2018; Kuk et al., 2019).

The individual SRT75% is summarized in **Figure 5**. The average SRT75% for each hearing aid condition (unaided, SAC, FAC) is shown in **Figure 6**. The mean unaided SRT75% was 9.43 dB. The mean SRT75% with FAC was 5.21 dB, while the mean SRT75% with SAC was 3.39 dB. A smaller SRT75% reflects better speech in noise performance. An independent *t*-test showed that the speech recognition in noise wearing either hearing aid was significantly improved over the unaided condition. However, there was no significant difference in performance between the two hearing aids. Thus, compression speeds did not significantly affect speech recognition in noise.

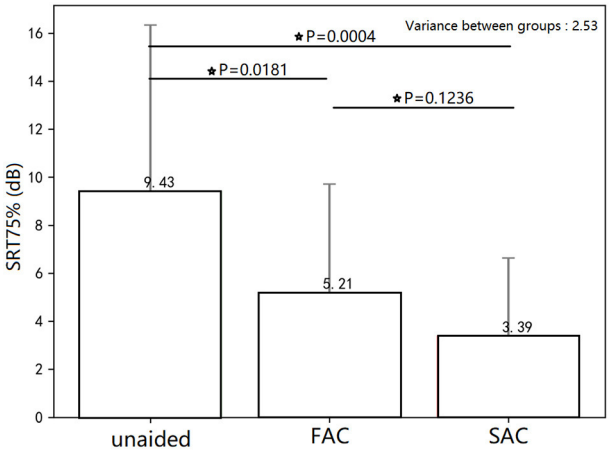

FIGURE 6 | Mean SRT75% for the three conditions. Speech recognition in noise wearing either hearing aid was significantly improved over the unaided condition. There was no significant difference in SRT75% between the two hearing aids. This * symbol means statistically significant.

Decision Tree Analysis of Compression Speed Candidacy

Both FAC and SAC hearing aids significantly improved the listeners' speech recognition of noise, but there was not a significant SRT75% difference between the two forms of compression speeds. While on a group level that may be the case, the varied unaided temporal resolution and speech in noise abilities of the presbycusic listeners suggest the possibility that compression speed may need to be customized to the individual's residual auditory abilities for maximum or optimal benefits. Thus, we turned to the use of a decision tree analysis (using python3.8 scikit-learn DecisionTreeClassifier). A decision tree is a supervised learning algorithm intended to produce a classification for a new object whose characteristics are known. Every inner node of the tree is labeled as a test, which compares the input attribute to a threshold, and every terminal node is labeled as a category. To obtain a classification for a new object whose attribute values are known, we could put it in the tree from the top node. When a terminal node is reached, the object's classification would have been defined (Geurts et al., 2009). In this analysis, subject performance in the unaided mode (along with the AP) was used as criterion measures to direct the selection of the optimal compression speeds. A detailed description of each step in the decision tree is provided.

First, we determined which compression speed may be more optimal for each subject. We measured the ratio of the aided SRT75% using FAC (fSRT75%) and that using SAC (sSRT75%) to compare their relative efficacy. As the 95% confidence interval on the SRT75% data was estimated at 0.156, 1 ± 0.156 was taken as the upper and lower limit of the confidence interval. Thus, when fSRT75%/sSRT75% > 1+0.156, SAC yielded a lower SRT and was judged better. When fSRT75%/sSRT75% < 1–0.156, FAC yielded a lower SRT and was thus better. When 1

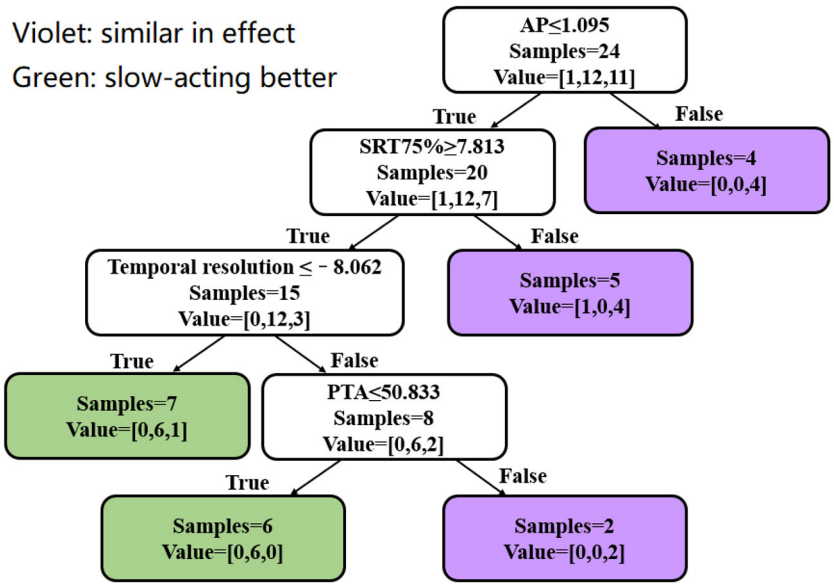

FIGURE 7 | Decision tree analysis. Violet represents a similar aided SRT75% between the two compression speeds. Green represents better SRT75% for SAC than FAC. Value = [A, B, C]: A is the number of subjects who performed better with FAC, B is the number of subjects who performed better with SAC, and C is the number of subjects where performance between FAC and SAC was similar.

TABLE 2 | Demographic characteristics and audiometry results of 10 additional subjects.

Age (year), median (Q1, Q3)	76.8, 78.5 (70.5, 83.8)
Male, *n* (%)	5 (50)
PTA (dB HL), median (Q1, Q3)	53.8, 55 (52.5, 56.3)
MoCA (point), median (Q1, Q3)	25.6, 25.5 (25, 27)
ECochG (-SP/AP %), median (Q1, Q3)	46.5, 43 (37.6, 56)
AP, median (Q1, Q3)	0.693, 0.685 (0.485, 0.84)

+ 0.156 ≥ fSRT75%/sSRT75% ≥ 1–0.156, the efficacy of the two hearing aids was judged similar. Based on this analysis, 1 subject performed better (ratio < 0.844) with FAC, 12 subjects performed better with SAC (ratio > 1.156), and 11 subjects had similar hearing performance between two compression speeds (ratio between 0.844 and 1.156). This finding may also explain the non-significant difference in SRT75% measured between SAC and FAC.

The decision tree analysis takes known factors that may affect the decision as inputs to generate the steps. According to previous studies, factors that may affect hearing aid performance include gender, age, cognitive level, cochlear ECochG (-SP/AP), SP, AP, PTA, unaided temporal resolution, and unaided SRT75%. These data were input to the model and the most significant factors that affected the decision included PTA, AP value, unaided modulation thresholds, and unaided SRT75%. The probable reasons for these factors were explained earlier in the methods. Of the 24 subjects included in the decision tree, 22 were correctly identified. The decision tree is shown in **Figure 7**.

The decision tree starts with the individual's AP. If the individual's AP is >1.095 μV, the aided SRT75% obtained with SAC and FAC would be similar. Four subjects were identified in this step. When AP ≤ 1.095 μV, the unaided SRT75% should be further compared. When the unaided SRT75% is <7.813 dB, the aided SRT between SAC and FAC should be similar. Five subjects were identified in this step with 4 showing no difference in aided SRT75% between SAC and FAC and 1 better aided SRT75% using FAC. If the unaided SRT75% is ≥7.813 dB, one should proceed to examine the unaided modulation thresholds. When the unaided modulation threshold is ≤-8.062 dB, SAC should yield a better SRT75% than FAC. Seven subjects were identified, of which 6 had a better aided SRT75% with SAC, while the remaining subject performed equally well with SAC and FAC. On the contrary, if the unaided modulation threshold is >-8.062 dB, the impact of hearing loss emerged. When the PTA is ≤ 50.833 dB, SAC yielded a better aided SRT75% than FAC. Six subjects were included in this step, and all had a lower SRT75% with SAC (than FAC). If the PTA is >50.833 dB, the effect of compression speed should be similar. Two subjects were included in this step, and both showed similar aided SRT75% for SAC and FAC.

Preliminary Validation Study on the Decision Tree Analysis

To verify the validity of the decision tree, 10 additional patients were enrolled (5 male patients and 5 female patients with an age range between 55 and 86 years). Their MoCA scores ranged from 21 to 28, and PTA ranged between 41.7 and 60 dB HL. The same experimental procedure, as mentioned earlier, was followed. The demographic characteristics and audiometric results of subjects are shown in **Table 2**.

The data of these 10 subjects were included in the decision tree for verification. Nine subjects were correctly identified by the

decision tree, with a pass rate of 90%. The judgment process and results are shown in **Figure 8**.

DISCUSSION AND CONCLUSION

This study showed that the unaided temporal modulation thresholds were preserved using SAC but were degraded using FAC. Aided speech recognition threshold using a 75% criterion (SRT75%) was significantly better than the unaided SRT75%, but not so between SAC and FAC. The unaided SRT75%, unaided modulation thresholds, along with AP and PTA allowed us to perform a decision tree analysis that may help select the optimal compression speed for an individual listener reliably, using the aided SRT75% as a criterion of performance.

The unaided modulation thresholds reflect the auditory system's ability to code temporal information. Aging and/or hearing loss alone or in combination can further damage this ability and make decoding of such temporal information difficult. In this study, we have shown that the compression speed could further alter or degrade such ability. In particular, the use of FAC smears the temporal contrast between louder and softer parts of the input sounds to result in poorer modulation thresholds. The use of SAC, on the contrary, preserved the modulation threshold measured in the unaided mode. As modulation thresholds have been reported to reflect speech in noise ability, it would suggest that speech in noise ability, measured as the SNR to reach 75% correct identification, would be poorer with FAC than with SAC. While better SRT75% was observed with SAC than FAC, the difference was non-significant.

A plausible reason for the non-significant difference between SAC and FAC may be the mixture of subjects with different residual temporal resolution abilities in this study. If their residual ability is either good or poor, the results of the comparison may be more clear-cut in showing the advantage of one form of compression speed over the other. Indeed, the decision tree analysis revealed that only 11 subjects showed a clearer benefit with SAC and 1 subject showed a clearer benefit with FAC. Notably, twelve subjects were indifferent in their performance between SAC and FAC. Fewer subjects showing indifferent results or more subjects showing performance benefits with one compression speed would likely change our observations and conclusions.

In that regard, the decision tree analysis provided good insights into the choice of optimal compression speeds on an individual basis. Rather than concluding that one form of compression speed is universally optimal for all listeners with presbycusis, the decision tree allows one to consider various individual factors (such as AP, PTA, unaided SRT75%, and unaided modulation threshold) in order to select the most optimal compression speed on an individual basis. If the values reported in this decision tree are further validated in future studies, this could offer an avenue for finer selection of hearing aid parameters and ultimately further improve elderly patients' speech in noise performance with their hearing aids.

In this decision tree, AP is taken as the first judgment criterion. Patients with high AP amplitude have a similar SRT75% between FAC and SAC, while in some patients with lower AP, SAC can achieve a better SRT75%. The low AP amplitude of ECochG reflects cochlear synaptopathy or low

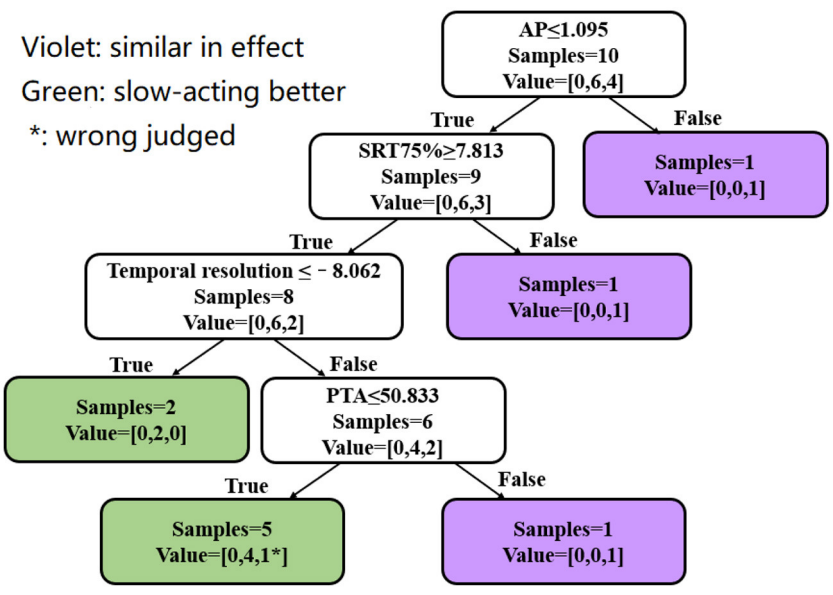

FIGURE 8 | Verification of the decision tree model. Violet represents a similar aided SRT75% between the two compression speeds. Green represents better SRT75% for SAC than FAC. "*" Represents a subject who was judged incorrectly. Value = [A, B, C]: A is the number of subjects who performed better with FAC, B is the number of subjects who performed better with SAC, and C is the number of subjects where performance between FAC and SAC was similar.

SR fiber dysfunction and is related to speech perception dysfunction in presbycusic patients. A study found that SAC can attain better speech recognition for children with auditory neuropathy, whose main lesion site is the auditory synapse (Narne and Vanaja, 2008). So, we inferred that SAC may facilitate signal transmission from inner hair cells to a nerve fiber in cochlear synaptopathy or low SR fiber dysfunction. Therefore, we reasonably suggest that among the patients with AP $\leq$ 1.095 μV, some of them have cochlear synaptopathy or auditory nerve dysfunction which may have been better served using SAC.

While we are motivated by the current findings of this study, we also recognized certain limitations to this study. First is the small sample size of patients ($n = 24$) that we used. Additional patients could increase the power of our observations and likely provide more robust criterion cutoff values in our decision tree analysis. Second, compression speed is only one important parameter in a compression hearing aid. The compression ratio, or the availability of other signal processing algorithms like noise reduction and directional microphones, could also affect the reported benefit and/or satisfaction toward the hearing aids. A more robust decision tree may also consider those factors. Third, our criterion of "more benefit" is simply the ratio of the SRT75% measured with FAC and SAC. Indeed, a lower SRT75% reflects better speech understanding of noise and is a good measure of benefit. However, other measures of performance such as sound quality, or an SRT at other criteria such as 50% or 90%, may also be a good metric to examine relative performance/benefit. Finally, all participants in this study had moderate-to-severe hearing loss. This may limit the generalizability of the results of the decision tree to other degrees of hearing loss. More subjects with varied hearing levels may be helpful to determine the impact of hearing loss (PTA) on the decision.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study were supplied by Peking University First Hospital under license and so cannot be made freely available. Requests for access to these data should be made to M.D. Zhang (yizhangsyx@163.com).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Biomedical Research Committee of the Peking University First Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL, YiZ, and JC conceived the study. YL, YiZ, JC, and YaZ developed the study design. YiZ, YaZ, and BS conducted the data wrangling. YL and YiZ drafted the article and conducted the analysis. YL, YiZ, and BS made important contributions to the interpretation of data. All authors contributed to the article and approved the submitted version.

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The effect of aging on context use and reliance on context in speech: A behavioral experiment with Repeat–Recall Test

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Purpose: To elucidate how aging would affect the extent of semantic context use and the reliance on semantic context measured with the Repeat–Recall Test (RRT).

Methods: A younger adult group (YA) aged between 18 and 25 and an older adult group (OA) aged between 50 and 65 were recruited. Participants from both the groups performed RRT: sentence repeat and delayed recall tasks, and subjective listening effort and noise tolerable time, under two noise types and seven signal-to-noise ratios (SNR). Performance–Intensity curves were fitted. The performance in SRT50 and SRT75 was predicted.

Results: For the repeat task, the OA group used more semantic context and relied more on semantic context than the YA group. For the recall task, OA used less semantic context but relied more on context than the YA group. Age did not affect the subjective listening effort but significantly affected noise tolerable time. Participants in both age groups could use more context in SRT75 than SRT50 on four tasks of RRT. Under the same SRT, however, the YA group could use more context in repeat and recall tasks than the OA group.

Conclusion: Age affected the use and reliance of semantic context. Even though the OA group used more context in speech recognition, they failed in speech information maintenance (recall) even with the help of semantic context. The OA group relied more on context while performing repeat and recall tasks. The amount of context used was also influenced by SRT.

KEYWORDS

context use, reliance on context, aging, working memory, speech understanding

Introduction

Speech recognition requires listeners to access phonological information and match it to its representation from semantic long-term memory (Ronnberg et al., 2019) and integrates these representations into meaningful and comprehensible sentences (Schurman et al., 2014). Both auditory and cognition systems play important roles during communication (Arlinger et al., 2009). However, aging could affect both auditory and cognitive processing in elderly listeners, manifested with effortful listening and even communication avoidance, especially under noisy conditions. One cognitive skill that could support communication in such environments is the ability to use context (Sheldon et al., 2008; Benichov et al., 2012).

Context is a general term of cues, including linguistic information like semantics, lexicon, syntactic structure, speech rate, and emotional information. It facilitates speech understanding by narrowing the lexicon search space (Janse and Jesse, 2014), guessing the missing information (Kathleen Pichora-Fuller, 2008), and accelerating word retrieval (Kave and Goral, 2017), to partially compensate for the noise interference (Janse and Jesse, 2014) and lexicon ambiguity (Kathleen Pichora-Fuller, 2008). The ability to use context is affected by the individual's auditory-cognitive ability, including short-term/working memory (Zekveld et al., 2013; Gordon-Salant and Cole, 2016), semantic long-term memory (Ronnberg et al., 2019), vocabulary knowledge from crystal intelligence (Salthouse, 2012), and the external sound environment(Winn and Moore, 2018; Signoret and Rudner, 2019), such as the type of background noise and signal-to-noise ratios (SNR).

Age affects the use of context; however, the extent of this effect is not clear. It has been shown that crystal intelligence, which provides vocabulary and linguistic knowledge to construct and utilize context, is preserved and even improved with age (Salthouse, 2010). One can say that older adults are quite adept at and skilled in using context because they rely on it to solve their daily communication difficulties (Dubno et al., 2000; Grady, 2000). On the other hand, the process of using context taps into cognitive functions like working memory (WM) (Janse and Jesse, 2014) that may decline with age. WM helps listeners use context to constrain the semantics of speech representation and accelerate semantic integration (Zekveld et al., 2011) to compensate for the increased processing needs when the signal is degraded (Zekveld et al., 2012; Janse and Jesse, 2014; Ronnberg et al., 2019). Thus, mixed results were seen when examining the effect of age (Ronnberg et al., 2019). For example, some studies concluded that the elderly used more context than, or at least as much as, their younger counterparts during speech recognition tests in quiet and in noise (Wingfield et al., 1994; Dubno et al., 2000; Sheldon et al., 2008). Other studies, such as Jiang et al. (Jiang et al., 2017), found that younger adults may use more context than older adults during sentence recognition in noise.

The mixed results of aging on context use may originate from the different noise conditions used in the various studies as well. As stated earlier, construction and utilization of context rely on the quality of speech signal (Pichora-Fuller et al., 1995). It has been shown that context would assist speech recognition only when the SNR becomes low but not too low (Schiller et al., 2020). When the SNR is extremely favorable, context is not needed for recognition because of the high quality of the speech signal (Pichora-Fuller et al., 1995; Nagaraj, 2017). As to noise types, Van Engen et al. (Van Engen et al., 2014) and Nittrouer et al. (Nittrouer and Boothroyd, 1990) found that babble noise is more difficult than steady-state noise because of informational masking. To minimize the impact of SNRs and noise types, Kuk et al. (Kuk et al., 2020, 2021) developed a Repeat–Recall Test (RRT) as the metric to examine context use over a range of SNRs and several noise conditions.

The RRT is a more comprehensive way to assess semantic context use. It is a sentence test that includes a Repeat and a Recall task. The Repeat task is an immediate recall task that asks participants to repeat the sentence immediately after hearing it. Performance on the Repeat task mainly relies on surface phonological morphosyntax information and short-term memory (Rummer and Engelkamp, 2003; Campoy and Baddeley, 2008; Tan and Ward, 2008; Polisenska et al., 2014). The Recall task is a time-limited (1 min) delayed (15 s after sentences presentation) free-recall task. It taps into more semantic interpretation and language processing (Polisenska et al., 2014), such as rehearsal and grouping strategy (Cowan, 2001; Bunting et al., 2006). Both Repeat and Recall tasks can be used to assess semantic context use (Kuk et al., 2020). High- and low-context sentences are created using the same words and syntactical structure. A high-context (HC) sentence is semantically and syntactically correct. A low-context (LC) sentence is created from the HC sentences within the same list by moving the keywords randomly across sentences so that the sentences are no longer meaningful but are still syntactically the same. Subjective listening effort (LE) and noise tolerable time (TT) are also assessed in the RRT. The difference in performance between high- and low-context sentences represents semantic context use (CU).

In the current study, we used the Chinese-RRT to examine how age would affect semantic CU and how this could be further influenced by test conditions. We hypothesized the following: (1) Age would influence CU in four RRT tasks and the reliance on context. (2) Noise conditions would also influence CU and the reliance on context. (3) CU and the reliance on the context under different speech recognition rates (or SNRs) might be different.

Materials and methods

Participants

Two groups of normal-hearing adults were recruited online *via* the Department's website. Fifty-four participants between 18 and 25 years of age (21.47 ± 2.20) were recruited into the young adult (YA) group. Fifty-two participants between 50 and 65 years of age (55.79 ± 5.23) were recruited into the older adult (OA) group. All the participants were native Mandarin speakers with audiometric thresholds < 25 dB HL from 250 to 8,000 Hz (pure tone average of YA: 10.03 ± 4.21 dB HL, OA: 20.84 ± 4.47 dB HL) and normal tympanograms. Their speech reception thresholds were tested with the Chinese HINT test, and the averages were −5.04 ± 0.88 dB for YA and −4.20 ± 0.79 dB for OA. All participants scored higher than 26 on the Montreal Cognitive Assessment (MoCA) and had over 5 years of formal education. No previous neurological diseases or long-term untreated chronic diseases were reported.

This study was approved by the Ethics Committee of the Peking University First Hospital (#2020-095). All participants signed informed consent and were financially reimbursed for their participation.

Description of the Chinese Repeat–Recall Test

The Chinese version of the RRT was created following the same procedures as the English version (Slugocki et al., 2018; Kuk et al., 2021). It has two themes: Food and Cooking and Daily Lives, targeting a third- to fourth-grade reading level. In each theme, seven lists, each with six sentences, were available. The high-context sentences were constructed with 9–12 Chinese words per sentence, each containing 3–4 keywords. All the keywords belong to Popularized Graded Words in the classification of syllabic Chinese words for International Chinese Education. A total of 20 keywords were scored in each list of six sentences. The low-context sentences were created by reassigning the keywords of high-context sentences to other sentences within the same list while maintaining the syntactic structure of the sentences. Examples of two of the high-context sentences in a list of six sentences: **香甜**的**点心**是用**蜂蜜**做的(**Sweet snacks** are made of **honey**)and **树**上的**橘子 成熟**了(The **orange** on the **tree** is **ripe**). Examples of two of the low-context sentences in a list of six sentences:**成熟**的**树**是用**橘子**做的(**Ripe tree** are made of **orange**) and 点心上的**蜂蜜 香甜**了(The **snack** on the **honey** is **sweet**). The whole example list is shown in the **Supplementary Material**. The sentences were recorded by a native Chinese female professional announcer in a standard soundproof room. The speech materials were equalized to have the same root-mean-square (rms) amplitude. Speech materials were presented at a fixed 75 dB SPL in all conditions.

Two types of background noise [Two-Talker Babble (TTB) and Speech-Shaped Noise (SSN)] were also available. TTB was created by mixing the speech (from an audiobook) read aloud by two female announcers and equalizing their maximum rms level and was presented from the front (0 degrees). The SSN was created by filtering a broadband noise with a filter that has the same long-term spectrum as the speech materials and was presented from the back (180 degrees). The noise level was varied to result in SNRs of −10, −5, 0, 5, 10, 15 dB, and quiet. All the stimuli could be acquired from the online **Supplementary Material**.

Repeat–Recall Test procedure

The test was performed in a sound-attenuated booth (ambient noise level <30 dB A). Speech and noise stimuli were presented *via* loudspeakers (Yamaha HS5) placed 1 m in front and behind the participant, at ear level. Instructions on the test were provided and the participants were trained with a non-test list at SNR = 10 dB before data collection. The order of RRT themes (2) and noise types (2) were counterbalanced across participants. Each of the seven sentence lists was tested at a different SNR in random order.

The test flow was the same as the English version (details in **Supplementary Figure 1**). Participants repeated each sentence after it was presented. Only keywords were scored when repeated correctly. The time interval between sentences was fixed at 2 s. After all six sentences were repeated, participants paused for 15 s and were instructed to recall as many of the sentences (or fragments of them) as they could within a minute. Only keywords that were repeated correctly during the Repeat phase were credited during Recall Keywords recalled correctly were scored. Afterward, participants were asked to rate how effortful it was for them to hear the sentences in the specific noise condition, which was also known as Listening Effort (LE). To evaluate LE, a visual analog scale (VAS) from 1 to 10 was used, with "1" as the least effortful and "10" as the most effortful. A rating of "11" was allowed if participants gave up because of the extremely noisy condition. Afterward, participants estimated the amount of time (in minutes) they were willing to spend communicating under the specific test condition, which is also known as Tolerable Time (TT). The low-context sentences were always presented before the high-context sentences to minimize any learning effect. A total of 28 trials (2 noises * 7 lists (SNRs) * 2 context conditions) were completed in one 1-h session. Rests were provided whenever needed to make sure both age groups, especially OA, would keep their attention and not be fatigued.

Data processing and statistical analysis

In the current study, CU was calculated as the difference between high- and low-context sentences. Since Repeat and Recall were scored as percent-correct, CU of Repeat and Recall were also transformed into rationalized arcsine unit (RAU) for further analysis (Studebaker, 1985). As CU was a difference-based index, a higher-context performance and a lower-context performance may lead to a similar CU, but with a different interpretation or implication. A high-context sentence represents a regenerated lexicon combination with helpful semantic (Potter and Lombardi, 1990). A low-context sentence simulates a word string relying on phonological and semantic representations (Haarmann et al., 2003). We also introduced another index: Proportion of CU (PCU) for Repeat and Recall separately. PCU was calculated as the proportion of CU to high-context scores (both CU and high-context scores were raw data without transforming to RAU), to measure how much one relied on context when repeating and recalling high-context sentences.

The Performance-Intensity (PI) curves of Repeat, Recall, LE, and TT were first simply drawn with the primary data. Then, smooth PI curves were fitted in the same way as done by Yang et al. (Zhigang Yang, 2007). The smooth curves of Repeat and Recall drawn through these points were logistic functions of the form

$$y = \frac{100}{1 + e^{-\sigma(x-\mu)}}$$

The smooth curves of LE drawn through these points were logistic functions of the form

$$y = \frac{10}{1 + e^{-\sigma(x-\mu)}}$$

The smooth curves of TT drawn through these points were logistic functions of the form

$$y = \frac{120}{1 + e^{-\sigma(x-\mu)}}$$

For all these curves, y was the probability of correctly repeating or recalling the keyword, x was the SNR corresponding to y, μ was the SNR corresponding to 50% correct on the psychometric function, and σ determined the slope of the psychometric function. The parameters (μ and σ), which were used to generate the curves in **Supplementary Figures 2, 3**, minimized Pearson's χ^2 goodness of fit of the model to the data. Quiet was treated as SNR = 30 dB when fitting the curves. SNRs corresponding to 50% (SRT50) and 75% (SRT75) speech recognition rate of high-context sentences in the Repeat task was calculated. Then, the corresponding performances for Repeat in low-context, Recall, LE, and TT in both high- and low-context were identified under the two SNRs. P/CU(Repeat$_{50\%/75\%}$), P/CU(Recall$_{50\%/75\%}$), CU(LE$_{50\%/75\%}$), and CU(TT$_{50\%/75\%}$) were calculated in the same way as aforementioned using the raw data.

The SPSS 25.0 software was used for the data analysis. A mixed-design was adopted with age groups as between-subject factors, while noise types, SNRs, and context as within-subject factors. Due to the skewed distribution of the data and repeated measurement, Generalized Linear Mixed Model (GLMM) was first applied to analyze the fixed (and interaction) effects of context (high vs. low) and age (younger vs older) to target variables: Repeat (in RAU), Recall (in RAU), and TT with random effects included an intercept for each participant. LE was a rank variable so that Generalized Estimated Equation (GEE) was performed to analyze the fixed effects. The effects of Age groups and Noise types on the target variables (CU (Repeat, Recall, and TT) and PCU (Repeat and Recall)) were also analyzed with GLMM, with random effects included as intercepts for each participant. Target variable CU(LE) was analyzed with GEE similarly. Factors with significant fixed effects were further analyzed for interaction effects. All the GLMM and GEE analyses were corrected for multiple comparisons using sequential Bonferroni. Degrees of freedom was fixed for all tests with a residual method. Independent sample t-tests were performed to further compare differences between groups at separate SNRs. Wilcoxon tests were performed to check whether P/CU under SRT50 was significantly different from that under SRT75 in the same age group. Mann Whitney U tests were performed to check whether P/CU in OA was significantly different from that in YA under the same SRT condition. Outliers were identified using a Box plot in SPSS and were excluded when performing the tests. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Performance-Intensity functions of Repeat–Recall Test and P/CU

Figure 1 displays the PI functions of RRT in the two age groups (two contexts and two noise conditions) with raw data. P/CU were calculated and PI functions were displayed in **Figures 2, 3**. The fitted PI curves are shown in the **Supplementary Figures 2, 3**.

Context significantly affected all the four tasks in RRT (Repeat: $F_{(1,2966)} = 376.924$, $P < 0.001$; Recall: $F_{(1,2966)} = 1268.480$, $P < 0.001$; LE: Wald $\chi^2(1) = 187.394$, $P < 0.001$; TT: $F_{(1,2966)} = 169.258$, $P = 0.004$). It improved Repeat and Recall performance, lowered subjective listening effort, and increased tolerable time. Age also significantly affected Repeat, Recall, and TT (Repeat: $F_{(1,2966)} = 46.407$, $P < 0.001$; Recall: $F_{(1,2966)} = 706.315$, $P < 0.001$; TT: $F_{(1,2966)} = 8.380$, $P = 0.004$). The interaction between context and age was found to be significant (Repeat: $F_{(3,2964)} = 163.208$, $P < 0.001$; Recall: $F_{(3,2964)} = 872.296$, $P < 0.001$; TT: $F_{(3,2964)} = 59.543$, $P < 0.001$). These results confirmed

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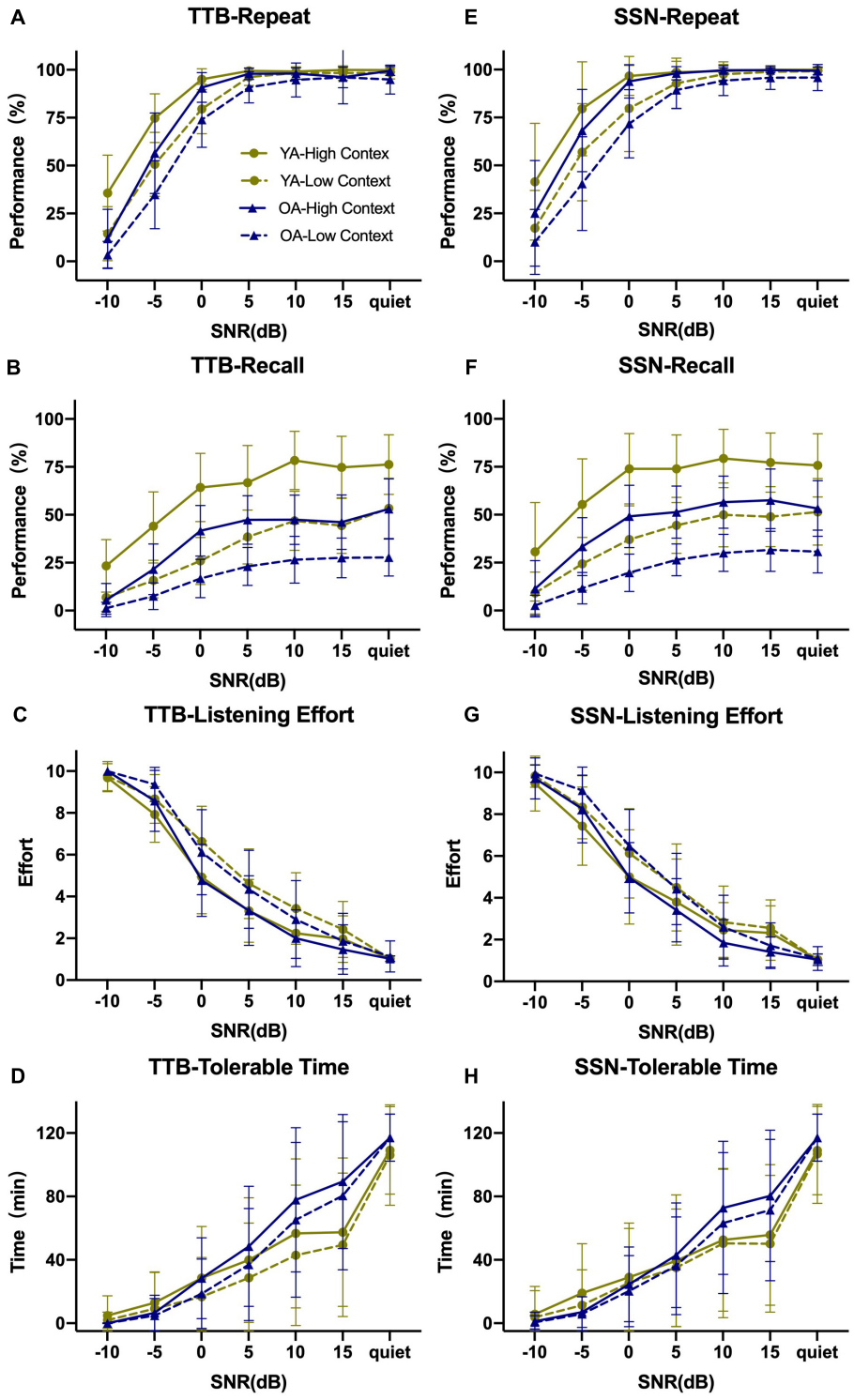

FIGURE 1
Overview of Repeat–Recall Test (RRT) performance in two-talker babble (TTB) and speech-shaped noise (SSN) for both age groups in seven SNRs. **(A–D)** Performance for TTB; **(E–H)** performance for SSN. Both performances for Repeat and Recall would increase as SNR became high, along with decreasing LE and prolonging TT. Recall seemed more insensitive to SNR comparing with Repeat and the curves were more smoothy than Repeat. Error bars represented one standard deviation.

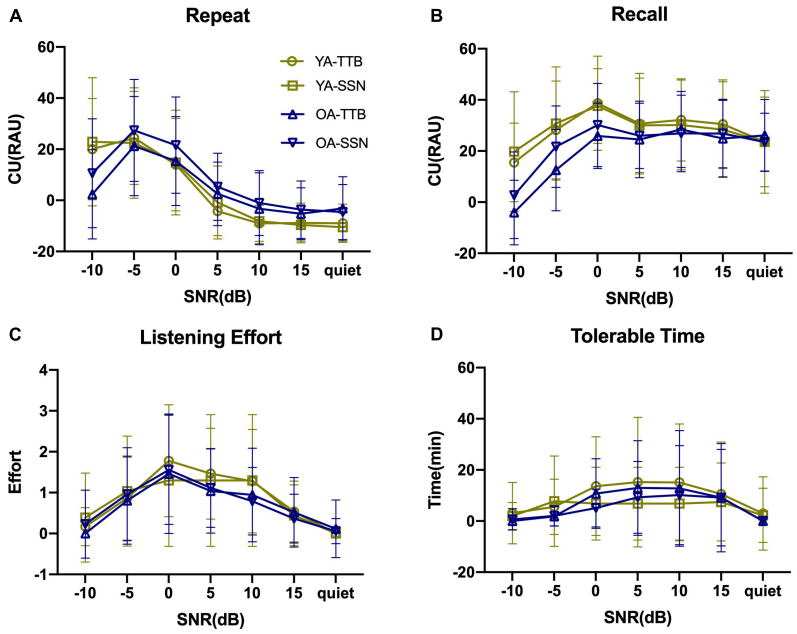

FIGURE 2
Context use (CU) of two age groups under two noise conditions and seven SNRs. **(A)** As for CU (Repeat), both age groups increased as SNR becomes worse and OA finally decreased when SNR = −10 dB, where YA could still hold the utilization of context. **(B)** As for CU (Recall), both age groups maintained their utilization of context when SNR > −5 dB and started to decrease at SNR = −5 and −10 dB. **(C)** As for CU (LE), LE was alleviated by context, and such alleviation arose as SNR became worse, peaking at SNR = 0 dB, and then decreased. **(D)** As for CU(TT), it seemed that it had a more stable trend as SNR changed. Error bars represented one standard deviation.

that participants in different age groups performed differently in different contexts (Table 1).

Age effect on P/CU

Age significantly affected CU on the Repeat, Recall, and TT tasks but not on the LE (Table 2). Results indicated that the YA group had a smaller CU (Repeat) ($F_{(1,1482)} = 49.291$, $P < 0.001$), a larger CU (Recall) ($F_{(1,1482)} = 69.083$, $P < 0.001$), and a longer CU (TT) ($F_{(1,1482)} = 14.001$, $P < 0.001$) than the OA group. In both high- and low-context conditions, LE was not significantly different between the two age groups (low-context: $\beta = 0.038$, Wald χ^2 (1) = 0.210, $P = 0.647$; high-context: $\beta = 0.086$, Wald χ^2 (1) = 0.921, $P = 0.337$). This also indicated that there was no significant fatigue in older adults during this 1-h session.

Results showed that the OA group had a higher PCU than the YA group on both Repeat ($F_{(1,1482)} = 58.623$, $P < 0.001$) and Recall ($F_{(1,1482)} = 38.783$, $P < 0.001$) tasks. This suggested higher reliance on the semantic context in OA than YA group (Table 2).

Noise types effect on P/CU

Noise types significantly affected CU (TT) with a longer time in TTB than SSN ($F_{(1,1482)} = 8.076$, $P = 0.005$). PCU (Recall) was larger in TTB than SSN ($F_{(1,1482)} = 5.755$, $P = 0.017$) (Table 2). However, noise types failed to affect P/CU (Repeat), CU (Recall), or CU (LE) ($P > 0.05$).

The interaction effect of age and noise type on CU (TT) was also significant ($F_{(3,1480)} = 6.671$,$P = 0.001$). CU (TT) was similar for the two noise types in OA (Coefficient = 0.768, $t = 0.942$, $P = 0.346$). However, it was significantly longer for TTB than for SSN in YA (Coefficient = 2.429, $t = 3.037$, $P = 0.002$). The interaction effect of age and noise type on PCU (Recall) was also significant ($F_{(3,1480)} = 14.637$,$P < 0.001$). PCU (Recall) was similar for the two noise types in OA (Coefficient = 0.021, $t = 1.303$, $P = 0.193$); however, it was significantly larger for TTB than for SSN in YA (Coefficient = 0.032, $t = 2.000$, $P = 0.046$). Details are shown in Supplementary Table 1.

P/CU at different speech recognition rates and signal-to-noise ratios

The SRT50 and SRT75 were identified by fitted PI curves: SRT50 was 5.71 ± 2.10 dB for OA-TTB, 7.50 ± 3.78 dB for OA-SSN, 8.59 ± 2.33 dB for YA-TTB, 8.47 ± 3.58 dB for YA-SSN. SRT75 was 3.52 ± 1.93 dB for OA-TTB, 5.21 ± 3.01 dB for OA-SSN, 5.44 ± 1.73 dB for YA-TTB, 6.35 ± 3.78 dB for YA-SSN.

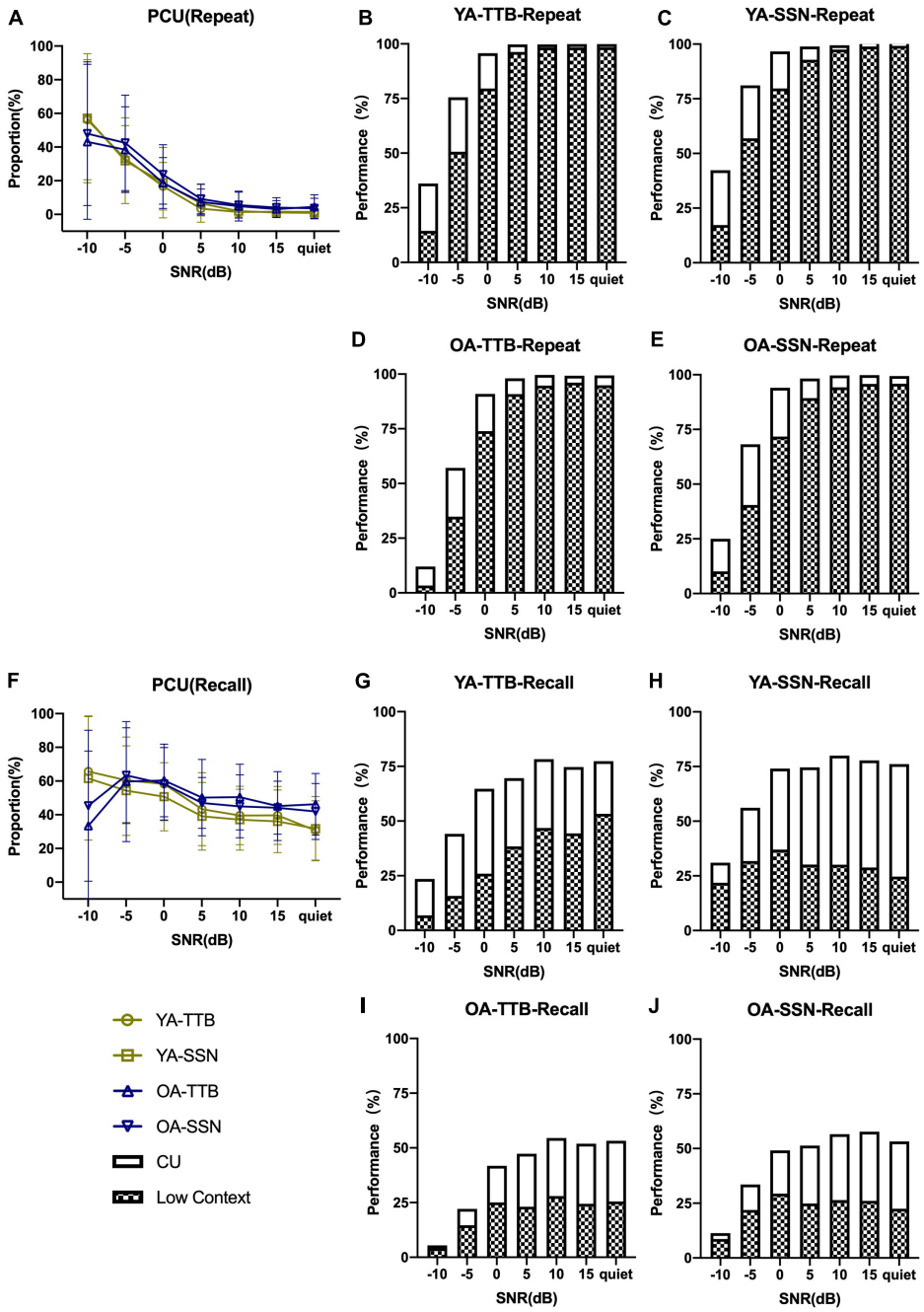

FIGURE 3
Proportion of CU in Repeat and Recall of two age groups under two noise conditions and seven SNRs. **(A)** PCU (Repeat) gradually rose as SNR became even worse. **(B–E)** PCU (Repeat) in two age groups under two noise types. **(F)** PCU (Recall) also rose as SNR decrease but in a much smooth trend, and OA failed to rely on context any more in SNR = −10 dB, where acoustic signals were degraded seriously. **(G–J)** PCU(Recall) in two age groups under two noise types. Hollow bars represented CU and grid represented low-context performance. The combination of the two represented the performance of high-context. Error bars represented one standard deviation.

For both age groups, the results indicated that in TTB, CUs in SRT50 were significantly lower than their counterparts in SRT75 with $P < 0.05$ (Figure 4 and Table 3). PCU ($Repeat_{50\%}$) was significantly higher than PCU ($Repeat_{75\%}$) for both age groups. PCU ($Recall_{75\%}$) was similar to PCU ($Recall_{50\%}$) in both age groups. In SSN, CUs in SRT50 were significantly lower than their counterparts in SRT75 with $P < 0.05$ (Figure 5 and Table 3). PCU of OA was the same in both SRTs. However, in YA, PCU ($Repeat_{50\%}$) was significantly lower than PCU ($Repeat_{75\%}$).

TABLE 1 Fixed effects of context, age group, and interaction effects to RRT tasks.

		Context	Age	Context*Age[a]
Repeat	F	376.924***	46.407***	163.208***
	df1	1	1	3
	df2	2966	2966	2964
Recall	F	1268.480***	706.315***	872.296***
	df1	1	1	3
	df2	2966	2966	2964
LE	Wald χ^2	187.394***	0.560	–
	df	1	1	–
TT	F	169.258***	8.380**	59.543***
	df1	1	1	3
	df2	2966	2966	2964

[a]Only factors with significant fixed effects will be further analyzed with interaction effects. $^{**}P < 0.01$, $^{***}P < 0.001$.

TABLE 2 Fixed effects and interaction effects to CU and PCU.

		Age	Noise type	Age*Noise type[a]
CU(Repeat)	F	49.291***	0.033	–
	df1	1	1	–
	df2	1482	1482	
CU(Recall)	F	69.083***	1.072	–
	df1	1	1	–
	df2	1482	1482	
CU(LE)	Wald χ^2	0.184	3.386	–
	df	1	1	–
CU(TT)	F	14.001***	8.076***	6.671**
	df1	1	1	3
	df2	1482	1482	1480
PCU(Repeat)	F	58.623***	0.404	–
	df1	1	1	–
	df2	1482	1482	
PCU(Recall)	F	38.783***	5.755*	14.637***
	df1	1	1	3
	df2	1482	1482	1480

[a]Only factors with significant fixed effects will be further analyzed with interaction effects. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

The results also showed that under both SRT50 and SRT75, CU ($Recall_{50\%/75\%}$) was significantly higher in YA than OA in both noise types ($P < 0.05$). Moreover, in SSN, P/CU($Repeat_{75\%}$) was higher in YA than OA ($P < 0.05$). Details are shown in **Table 4**.

Independent *t*-tests were performed to evaluate the difference in P/CU (Repeat, Recall) between two age groups across SNRs while collapsing performances from both noise conditions (**Supplementary Table 2**). The results showed that (1) CU (Repeat) for OA was significantly higher than that for YA at SNR $\geq$ 5 dB ($P < 0.001$). Differences between age groups disappeared at SNR = 0, 5 dB ($P > 0.05$). When SNR = −10 dB, CU (Repeat) for OA was significantly lower than that for YA (t (104) = 4.974, $P < 0.001$). (2) CU (Recall) for the two age groups was similar when SNR $\geq$ 10 dB ($P > 0.05$), but higher for YA than OA at SNR $\leq$ 5 dB ($P < 0.05$). (3) Both PCU (Repeat) and PCU (Recall) for OA were significantly higher than those for YA when SNR $\geq$ 5 dB ($P \leq 0.01$). PCU(Recall) was significantly lower in OA when SNR = 10 dB (t (89.573) = 4.13, $P < 0.001$).

Discussion

In the current study, we examined semantic context use (CU) and reliance on semantic context (PCU) in two age groups under two noise types on the various measures of the Chinese RRT (Repeat, Recall, Listening Effort, and Tolerable Time) over a range of SNRs. As expected, CU and PCU were significantly influenced by age. OA used more semantic context in the Repeat task and relied more on the semantic context in both Repeat and Recall tasks than YA. In contrast, YA used more semantic context in the Recall and Tolerable Time tasks and relied less on semantic context than OA. Context use in SRT50 was significantly lower than that in the SRT75 for both the age groups in the four RRT tasks. The reliance on the context in the Repeat task was also higher in SRT50 than in SRT75. At the same SRT, context use in Repeat (SRT50 in SSN only) and Recall tasks were significantly higher in YA than those in OA.

Cognitive processes of semantic context use in repeat and recall tasks

The Repeat task can be viewed as a process of context acquisition, where speech signals that provide (or do not) a semantic context are gathered (Rummer and Engelkamp, 2003; Campoy and Baddeley, 2008; Tan and Ward, 2008; Polisenska et al., 2014). As such, it is more susceptible to the impact of poor SNR than Recall when SNR $\leq$ 0 dB (**Figures 1A,E** vs. **Figures 1B,F**, respectively). In the current study, when SNR > 0 dB, minimal CU was observed for Repeat (Pichora-Fuller et al., 1995; Nagaraj, 2017). The Recall task is a process of semantic context maintenance (Barrett et al., 2004), which is less affected by SNR (once it is audible), but more affected by cognitive function than Repeat. Indeed, CU (Recall) was maintained at a high level above SNR = 0 dB. This was also consistent with the nature of Recall as semantic interpretation and language processing (Polisenska et al., 2014).

We believe that both Repeat and Recall tasks benefit from WM since it is a fundamental cognitive function related to speech understanding (Baddeley, 2012) and online sentence processing (Evans et al., 2015). The Ease of Language Understanding (ELU) model (Ronnberg et al., 2019) acknowledges that when a mismatch between phonological and semantic information occurs during the explicit process, WM

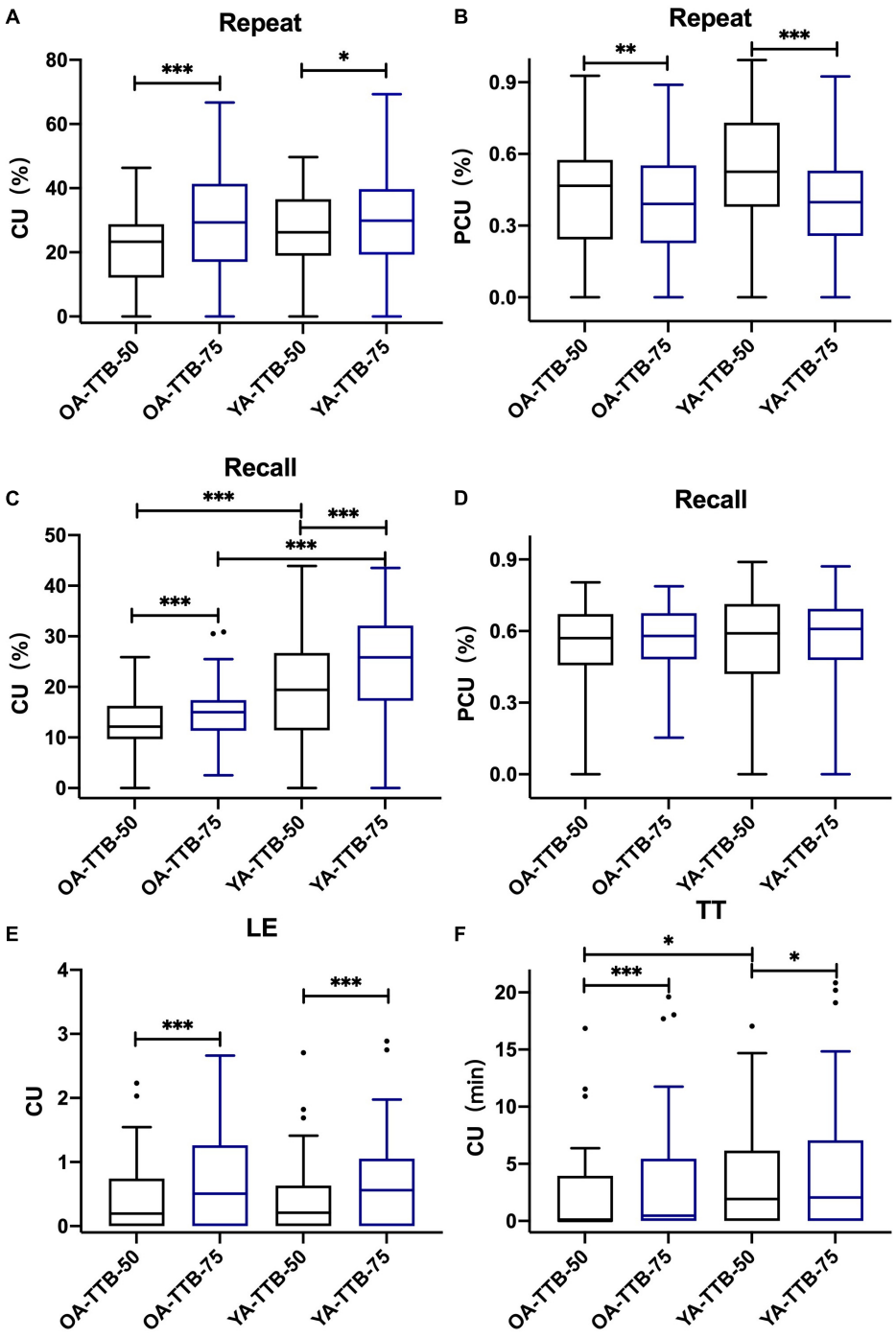

FIGURE 4
P/CU performances under two SRTs in two age groups in TTB. **(A)** CU ($Repeat_{50\%/75\%}$), **(B)** PCU ($Repeat_{50\%/75\%}$), **(C)** CU($Recall_{50\%/75\%}$), **(D)** PCU ($Recall_{50\%/75\%}$), **(E)** CU ($LE_{50\%/75\%}$), **(F)** CU ($TT_{50\%/75\%}$). All the figures were Boxplot. The top and bottom lines of a column represented the maximum and minimum values of the data, respectively. The top and bottom lines of the box represented the third quartile and the first quartile, respectively, and the line in the middle of the box represents the median of the data. Black circles represented outliers. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

helps to construct a supportive context. Because WM is a limited resource, it is shared between information processing and storage (Baddeley, 2012). During the Repeat task of context acquisition, more WM is allocated to processing. During the Recall task of context maintenance, more WM is allocated to storage (Tan et al., 2017). CU on the two tasks would likely

TABLE 3 Differences between SRT75 and SRT50 in two age groups under two noise types.

		TTB	SSN
		Z	Z
OA	$CU(Repeat_{75\%})$-$CU(Repeat_{50\%})$	−4.406***	−5.883***
	$PCU(Repeat_{75\%})$-$PCU(Repeat_{50\%})$	−2.681**	−1.530
	$CU(Recall_{75\%})$-$CU(Recall_{50\%})$	−6.215***	−6.193***
	$PCU(Recall_{75\%})$-$PCU(Recall_{50\%})$	−1.153	−0.301
	$CU(LE_{75\%})$-$CU(LE_{50\%})$	−4.119***	−5.012***
	$CU(TT_{75\%})$-$CU(TT_{50\%})$	−4.088***	−4.553***
YA	$CU(Repeat_{75\%})$-$CU(Repeat_{50\%})$	−2.333*	−4.016***
	$PCU(Repeat_{75\%})$-$PCU(Repeat_{50\%})$	−4.980***	−2.293
	$CU(Recall_{75\%})$-$CU(Recall_{50\%})$	−6.220***	−5.782***
	$PCU(Recall_{75\%})$-$PCU(Recall_{50\%})$	−1.084	−2.398*
	$CU(LE_{75\%})$-$CU(LE_{50\%})$	−5.359***	−4.402***
	$CU(TT_{75\%})$-$CU(TT_{50\%})$	−2.430*	−2.812**

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

be complementary (i.e., as one increases, the other decreases). Once resource demand exceeds its capacity limit, performance decreases. This may be evident from the complementary changes in CU for the Repeat and Recall tasks across SNRs from quiet to SNR = −5 dB. At SNR = −10 dB, CU was the poorest in the OA who are likely limited in WM.

How does age affect semantic context use and context reliance?

In the current study, we found that OA performed more poorly in the low-context sentences than YA in the Repeat task leading to a higher P/CU (Repeat) (low-context coefficient = −6.828; high-context coefficient = −1.183, $P < 0.001$; **Table 5** for statistic details). As repeating low-context sentences rely on phonological maintenance and rehearsal (Bailey et al., 2009), the declined processing speed (Salthouse, 2000; Arlinger et al., 2009) in OA makes it harder for them to match phonological information to representation accurately and efficiently without semantic context. Due to the relatively low WM capacity (confirmed by the Backward Digit Span task, where the performance of YA was 8.59 ± 2.25 and that of OA was 5.75 ± 1.74, t (104) = 7.204, $P < 0.001$), declined semantic short-term memory (Haarmann et al., 2003) in the OA may be another explanation. This explanation also aligns with the finding that when the context is unavailable, the reliance on working memory increases (Nagaraj, 2017), and participants with higher WM can better handle low-context sentences (Moradi et al., 2014) than those with lower WM. This result is consistent with a previous study by Sheldon et al. (2008), which showed that context helped reduced the number of noise-vocoded bands needed for 50% word recognition, and this reduction was more in OA than YA. Aydelott et al. (2010) showed that under quiet conditions, OA used more context than YA in word recognition in quiet. Our study further expanded the range of SNR and explained how CU (Repeat) is influenced by SNR. When SNR ≥ 5 dB, OA had significantly higher CU (Repeat) than YA; this difference disappeared as SNR became poorer (SNR = 0, 5 dB) and reversed when SNR = −10 dB. This suggested that YA could use more semantic context only when it is needed at unfavorable SNR. This observation was supported by the PCU (Repeat) PI function that showed a steep negative slope at SNR < 0 dB. This also implied that CU (Repeat) relies on the demand for semantic context, and if the test condition was unfavorable, YA could use context equally or more than OA (Dubno et al., 2000; Aydelott et al., 2010; Jiang et al., 2017).

In the current study, we also found that OA performed poorer than YA in the Recall of high-context sentences. This led to lower CU (Recall) and higher PCU (Recall) in OA than YA (low-context: Coefficient = 17.082; high-context: Coefficient = −22.520, $P < 0.001$; **Table 5** for statistic details). Recall of high-context sentences relies on semantic maintenance (Potter and Lombardi, 1990; Bailey et al., 2009) and can be considered understanding a regenerated lexicon combination with helpful semantic (Potter and Lombardi, 1990). It has been proved that WM helps semantic integration (Zekveld et al., 2011; Yang et al., 2020) by accelerating word retrieval (Unsworth et al., 2012), but was declined in our sample (compared to the YA sample). Besides, the semantic strategy also declines with aging (Haarmann et al., 2005). In addition, since OA is more easily distracted due to a lack of inhibitory control and attention (Hasher et al., 1991; Peelle et al., 2010; Salthouse, 2012), which can also benefit from WM (Baddeley, 2003; Barbas et al., 2018), the noise during the 15 s retention and the 1 min Recall process would increase the burden of maintaining information (both semantic context information from high-context sentences, and lexicon information from low-context sentences) for OA. YA with higher working memory may have more storage resources for even low-context recall. Accordingly, YA could use more semantic context than OA in Recall. Golomb et al. (2008) showed similar results that YA used more context to help visual recall of words than OA. As we expanded the SNR range, we found that the difference between age groups disappeared when SNR > 5 dB. This was because the noise was not distracting enough to interfere with context maintenance. Tun et al. (2002) also concluded that there was no difference between YA and OA in quiet conditions when recalling high-context text and low-context word strings. This means that when speech audibility is ensured, both groups could use semantic context similarly when recalling, even though OA may rely more on it. When SNR ≤ 5 dB, YA could make more use of semantic context than OA.

We failed to see the effect of age on CU (LE). This is in line with the result from Hunter et al. (Hunter and Humes, 2022), who interpreted that OA is quite an expert in context utilization, and this process seems to happen

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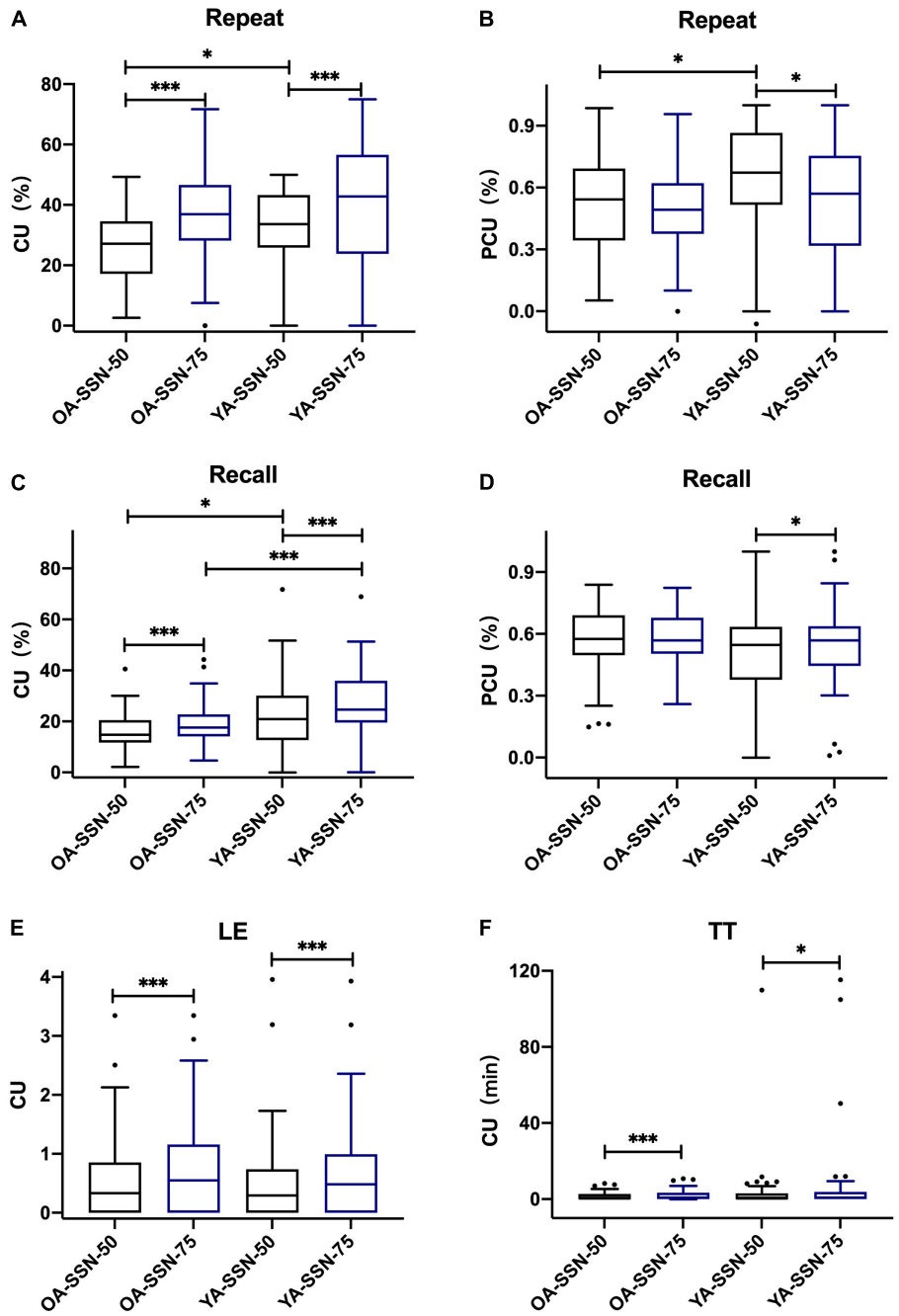

FIGURE 5
P/CU performances under two SRTs in two age groups in SSN. **(A)** CU ($Repeat_{50\%/75\%}$), **(B)** PCU ($Repeat_{50\%/75\%}$), **(C)** CU ($Recall_{50\%/75\%}$), **(D)** PCU ($Recall_{50\%/75\%}$), **(E)** CU ($LE_{50\%/75\%}$), **(F)** CU ($TT_{50\%/75\%}$). All the figures were Boxplot. The top and bottom lines of a column represented the maximum and minimum values of the data, respectively. The top and bottom lines of the box represented the third quartile and the first quartile, respectively, and the line in the middle of the box represents the median of the data. Black circles represented outliers. $^{*}P < 0.05$, $^{***}P < 0.001$.

automatically without consuming extra effort. Thus, the two age groups might reduce the same amount of LE when providing context.

We found that age affected CU (TT) and that semantic context would prolong noise tolerable time more in YA. This may suggest that OA are quite familiar with the suboptimal listening environment, and tolerable time is less affected by context (Pichora-Fuller and Singh, 2006) than in YA.

TABLE 4 Differences between two age groups in SRT50 and SRT75.

		SRT50	SRT75
		Z	Z
TTB	CU(Repeat)	−1.760	−0.095
	PCU(Repeat)	−1.760	−0.095
	CU(Recall)	−3.697***	−4.967***
	PCU(Recall)	−0.265	−0.638
	CU(LE)	−0.085	−0.330
	CU(TT)	−2.331*	−1.361
SSN	CU(Repeat)	−2.305*	−0.882
	PCU(Repeat)	−2.305*	−0.882
	CU(Recall)	−2.266*	−4.076***
	PCU(Recall)	−1.567	−1.024
	CU(LE)	−0.367	−0.480
	CU(TT)	−0.981	−0.673

*$P < 0.05$, ***$P < 0.001$.

TABLE 5 Interaction effects of age groups * Context in Repeat and Recall.

	OA-YA low context	OA-YA high context
	Coefficient	Coefficient
Repeat	−6.828***	−1.183***
Recall	−17.082***	−22.520***

***$P < 0.001$.

How does signal-to-noise ratio affect semantic context use and context reliance?

In the current study, CU in SRT75 was significantly higher than that in SRT50. This indicates that a relatively higher quality of speech signal was conducive to constructing a context and utilizing it in different tasks (Pichora-Fuller et al., 1995). Also, the reliance on context may also be lower, and this seemed to be more prominent in Repeat. Reliance on the context during Recall seemed less affected by SRT.

In SRT75, which is closer to the daily situation than SRT50, P/CU(Repeat$_{75\%}$) was similar in both age groups. This indicated that when restricting the amount of speech information one could get, semantic CU during speech recognition for young and old adults were nearly the same. This result was different from previous studies that concerned the same test SNR and neglected the different SRT in both age groups (Wingfield et al., 1994; Dubno et al., 2000; Sheldon et al., 2008). Therefore, the difference in CU may also arise from SRT. However, YA could use more context when recalling semantic information. This could be explained by the relatively higher working memory capacity of YA to maintain more semantic information. In SRT50, we found that the difference in CU in Recall still existed between the two age groups. Besides, P/CU(Repeat) in YA was higher than that in OA in SSN but not in TTB.

Conclusion

In the current study, we used the Chinese RRT to examine the effect of age on semantic context use and semantic context reliance under different test conditions and test items. We concluded that even though older adults may acquire more semantic context to help with repeating information, they still face difficulties in maintaining semantic context information for later recall. For both repeat and recall tasks, older adults tended to rely more on context. SRT influenced the performance of context use and reliance on the context in the two age groups, reminding us to pay attention to SRT in future research.

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 human participants were reviewed and approved by the Ethics Committee of the Peking University First Hospital. The participants provided their written informed consent to participate in this study.

Author contributions

JS collected the data, organized the database, performed the statistical analysis, and wrote the manuscript. ZZ, HL, CW, and YL contributed to the conception and design of the study. BS participated in the data collection and technical support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

BS was employed by Widex Hearing Aid (Shanghai) Co., Ltd.

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.924193/full#supplementary-material

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Age-Related Changes in Interaural-Level-Difference-Based Across-Frequency Binaural Interference

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Low-frequency interaural time differences and high-frequency interaural level differences (ILDs) are used to localize sounds in the horizontal plane. Older listeners appear to be worse at horizontal-plane sound localization to compared younger listeners, but little is understood about age-related changes to across-frequency binaural processing. This study investigated if the frequency dependence of across-frequency ILD processing is altered for older compared to younger listeners, which was done by using an across-frequency binaural interference task (when the interaural difference sensitivity for a target sound is decreased by a spectrally remote interfering sound with zero interaural differences). It was hypothesized that as listeners experience advancing age and age-related high-frequency hearing loss (i.e., presbycusis), they will demonstrate worse binaural performance and experience more across-channel binaural interference (because of age-related temporal processing deficits), and will increasingly be affected by interferers at lower frequencies (because of age-related hearing loss) when compared to younger listeners. There were 11 older (>65 yrs) and 20 younger (<30 yrs) listeners with normal to near-normal audiometric thresholds up to 2 kHz. They were tested using a left-right ILD lateralization discrimination task. Single-tone ILD discrimination thresholds and across-frequency binaural interference were measured at 0.5, 1, 2, 4, and 8 kHz. ILD thresholds and interference were about twice as large for older compared to younger listeners. Interferers ≤1 kHz produced 2–3 times as much across-frequency binaural interference for older compared to younger listeners. Hearing thresholds were significant predictors of single-tone ILD thresholds; in addition, both target and interferer hearing thresholds were significant predictors of binaural interference. The results suggest a reweighting of binaural information that occurs with advancing age and age-related high-frequency hearing loss. This evidence of plasticity may help explain some of the age-related changes in spatial-hearing abilities.

Keywords: binaural hearing, aging, hearing loss, interaural level differences (ILDs), across-frequency binaural interference

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INTRODUCTION

The prevalence of background noise in social situations is high. Communicating in non-quiet and acoustically complex listening environments is facilitated greatly by spatial hearing, particularly in younger listeners. In comparison, older listeners demonstrate diminished spatial-hearing benefits in background noise and report greater difficulty communicating in these situations (Srinivasan et al., 2016; Gallun and Best, 2020; Gallun et al., 2021). A portion of age-related auditory processing deficits manifest from high-frequency hearing loss (i.e., presbycusis), another portion may manifest from central or neural age-related temporal processing deficits (Anderson et al., 2018, 2021), and another portion may manifest from cognitive processing (for reviews, see Working Group on Speech Understanding Aging, 1988; Gordon-Salant et al., 2010; Helfer et al., 2020).

Focusing on human sound localization in the horizontal plane, the "Duplex Theory of Sound Localization" (Strutt, 1907) states that interaural time differences (ITDs) at lower frequencies (less than ∼1.5 kHz; Hartmann, 2021) and interaural level differences (ILDs) at higher frequencies are used for sound localization. The relative weighting of interaural information heavily favors low-frequency ITDs for sound localization (Wightman and Kistler, 1992; Macpherson and Middlebrooks, 2002). For pure tones presented in the free field, sound-localization and location-discrimination performance is a constant function of frequency, except that performance worsens between 1.5 and 3 kHz (Stevens and Newman, 1936; Mills, 1958). This may be because neither ITDs nor ILDs are conveyed well in this frequency region (Macaulay et al., 2010; Brughera et al., 2013). When presented over headphones, humans are sensitive to changes in ILDs at all frequencies and there is relatively equal ILD sensitivity across frequency (e.g., Brown and Tollin, 2021), despite the fact that ILDs are largest at higher frequencies (Feddersen et al., 1957; Hartmann, 2021). If there is an increase in ILD-based lateralization with increasing frequency, it is a small effect (Bernstein and Trahiotis, 2011; Goupell and Stakhovskaya, 2018b). The small or negligible ILD sensitivity frequency dependence is also consistent with physiological recordings (Jones et al., 2015). ILDs are first computed in the lateral superior olive of the superior olivary complex, and require temporally precise inputs on the order of milliseconds (Brown and Tollin, 2016; Franken et al., 2018; Ashida et al., 2021), similar to the temporal precision required of ITD processing in the medial superior olive (Goldberg and Brown, 1969; Yin and Chan, 1990).

The temporal precision to binaural neural encoding is affected by aging and hearing loss (Ross et al., 2007; Grose and Mamo, 2012; Ozmeral et al., 2016; Anderson et al., 2018; Eddins and Eddins, 2018; Eddins et al., 2018; Gallun et al., 2021). For example, sound localization in the vertical (Otte et al., 2013) and horizontal planes (Dobreva et al., 2011) appear to worsen with increasing age and hearing loss. ITD discrimination sensitivity (Strouse et al., 1998) and binaural temporal fine structure sensitivity (Eddins and Eddins, 2018; Füllgrabe and Moore, 2018; Füllgrabe et al., 2018) also decrease with increasing age. There appears to be stronger high-frequency rate limitations with increasing age for modulated high-frequency signals (Anderson et al., 2019). It could be that many of the binaural temporal processing deficits are partially related to age-related monaural temporal processing deficits (Grose and Mamo, 2012; Ihlefeld et al., 2015; Laback et al., 2017; Devries et al., 2022). Age-related decreases in ITD sensitivity and lateralization readily occur, whereas age-related decreases in ILD sensitivity and lateralization may be relatively smaller or negligible (Babkoff et al., 2002; Anderson et al., 2019).

While age-related performance degradation occurs across a wide array of hearing abilities, the brain might adapt as listeners lose access to different types of spatial information. Otte et al. (2013) hypothesized that listeners may shift their spectral filtering cue range for vertical plane localization from higher to lower frequencies with increasing age. The rationale included a functional role for listeners' pinna growing larger with age, which would physically shift the relevant cues to lower frequencies, where high-frequency age-related hearing loss would be less extreme. While their hypothesis was not supported, age-related changes to ITD and ILD processing for horizontal-plane localization can be similarly considered. On one hand, high-frequency age-related hearing loss would reduce access to the largest (Feddersen et al., 1957; Hartmann, 2021) and arguably most useful ILDs; on the other hand, age-related temporal processing deficits would reduce access to potent and heavily weighted low-frequency ITDs. Therefore, it may be that low-frequency ILD cues may become weighted more heavily because there is a greater reduction in ITD relative to ILD sensitivity (Eddins and Hall, 2010); however, this hypothesis concerning age-related changes to the frequency dependence of binaural processing has not yet been explored (Gallun, 2021).

Therefore, a study was performed to evaluate age-related changes to across-frequency ILD processing. This was done using an "across-frequency binaural interference" task (Mcfadden and Pasanen, 1976), where the listener is asked to discriminate or lateralize changing interaural differences in a target band and ignore the other remote and spectrally resolved interfering band that has fixed interaural information (i.e., there is conflicting binaural information across frequencies, such as a diotic or zero ILD interferer band). Interference occurs when the discrimination sensitivity or extent of lateralization decreases in the presence of the remote interferer, meaning the interaural information is combined across frequency channels at some point in the central auditory processing. These types of stimuli with a band with zero ILD and all bands with zero ITD are not experienced for natural sound sources outside the laboratory. One reason to use across-channel ILD processing is that it demonstrates a much stronger frequency dependence than occurs for single frequencies (Goupell and Stakhovskaya, 2018a; Rosen and Goupell, 2022); however, the across-channel ILD processing frequency dependence is not yet well-understood (Best et al., 2021). Another reason to use across-channel ILD processing is that the frequency dependence of ILDs are not as large and extreme as occurs for ITDs (Heller and Richards, 2010), which means that the frequency effects may be more inclined to reveal age-related changes. Finally, another reason to use across-channel ILD processing is that if there is an age-related shift of ILD weighting to lower frequencies, this

shifts the relative importance to a region where ILDs produced by the head are naturally smaller, and hence possibly less beneficial for spatial-hearing tasks. It was hypothesized that binaural performance would be worse and binaural interference would increase for older compared to younger listeners because of central changes independent of frequency, possibly related to age-related temporal processing deficits because all binaural comparisons require temporal precision. In addition, it was hypothesized that relatively more interference would occur for the lower frequency targets (e.g., <4 kHz) because of the onset of age-related high-frequency hearing loss.

MATERIALS AND METHODS

Listeners

Eleven older listeners (average age = 72 yr; age range = 67–80 yr; 8 females) were tested. All older listeners had relatively good hearing for their age with audiometrically normal to near-normal hearing at octave frequencies from 0.25 to 2 kHz, which was defined as ≤30 dB HL with interaural asymmetries ≤15 dB. Larger hearing thresholds were allowed at 4 and 8 kHz, with interaural asymmetries ≤20 dB at these frequencies. Because these listeners had relatively good hearing for their age, particularly at low frequencies, they were called older normal-hearing (ONH) listeners despite some having larger hearing losses at ≥4 kHz. An additional ONH listener started the experiment, but did not finish it and their data was omitted from the analysis.

Twenty younger normal-hearing (YNH) listeners (average age = 22 yr; age range = 20–27 yr; 15 females) were tested as a control group; the data were previously reported in Rosen and Goupell (2022). They met stricter hearing threshold criteria: ≤20 dB HL with interaural asymmetries ≤15 dB at octave frequencies from 0.25 to 8 kHz. The average hearing thresholds for all the listeners are shown in **Figure 1**.

The ONH listeners also performed a cognitive screening test (Nasreddine et al., 2005). They all had a score of ≥22 (average = 26.9, S.D. = 2.5), indicating at most a mild cognitive impairment (Dupuis et al., 2015; Cecato et al., 2016). Therefore, poorer performance for the ONH listeners was not likely a result of cognitive impairment. A screening score from one ONH listener was not available because of experimenter error.

Stimuli

The stimuli consisted of single target tones or target-interferer tone pairs presented at five frequencies of 0.5, 1, 2, 4, and 8 kHz. The tones were 300 ms in duration, had zero phase, and had a temporal raised-cosine ramp with a 10-ms rise-fall time applied. Tone pairs occurred simultaneously. Each tone was presented nominally at a level of 65 dB-A. Diotic level roving of ±10 dB (uniform distribution) was applied to the entire stimulus; in other words, the level roving did not introduce overall level differences across frequency. A non-zero ILD was applied to the target tones by increasing the level in dB in one ear by ILD/2 and decreasing the level in the other ear by ILD/2. The interfering tone was diotic, meaning it had zero ILD. Both targets and interferers had zero ITD. The target stimuli were audible and all listeners could perform the task for all conditions at these levels, even at 8 kHz, where some of the older listeners had high-frequency hearing loss. Stimuli had a sampling rate of 48.828 kHz. The stimuli were the same as in experiment 1 of Rosen and Goupell (2022).

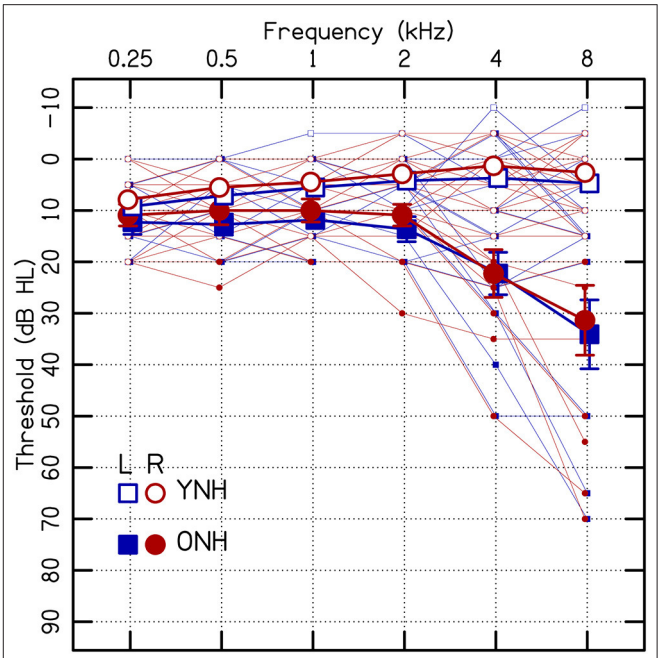

FIGURE 1 | Individual (small points) and average (large points) audiometric thresholds in dB (re: hearing level, HL). Error bars represent ±1 standard error of the listener mean. Some points have error bars smaller than the size of the point. ONH, older normal hearing; YNH, younger normal hearing.

Equipment

The experiment was completed in a double-walled sound-attenuating chamber (Industrial Acoustics Inc.; Bronx, NY). Listeners were presented stimuli and the experiment was controlled using MATLAB (the Mathworks; Natick, MA) on a personal computer. The stimuli were delivered by a real-time processor, programmable attenuator, and headphone buffer (System 3 RP2.1, PA5, HB7; Tucker-Davis Technologies, Alachua, FL) to a pair of insert earphones (ER2; Etomotyic, Elk Grove Village, IL). Insert earphones minimized issues with ear canal collapse for the ONH listeners. The equipment was the same as in experiment 1 of Rosen and Goupell (2022).

Procedure

Listeners controlled the experiment by interacting with a graphical user interface. They clicked a button to initiate a trial of an adaptive track. Each trial consisted of a two-interval left-right lateralization discrimination task. There was an interval that had a right-ear-favoring ILD and the other had a left-ear-favoring ILD, the direction of the ILD in the first interval randomly chosen with 50% *a priori* probability. The task was to report the perceived direction that the sound moved from the first to the second interval. After each trial, correct answer feedback was provided. The adaptive staircase procedure had 14 reversals. The

ILD decreased if there were three sequentially correct responses and increased for an incorrect answer (79.4% correct on the psychometric function; Levitt, 1971). For 14 reversals, each track usually required 50–80 trials to reach completion. The starting target ILD for a track was 20 dB, a difference that was obvious to the listeners because the target tone move from one the side of the head to the other while the interferer tone remained near the center of the head; the correct answer feedback resolved any confusion about the identity of the target frequency. The ILD step size became smaller as the adaptive procedure continued. The ILD step size was ±4 dB for trials up to the second reversal, was ±2 dB for trials up to the fourth reversal, was ±1 dB for trials up to the sixth reversal, and was ±0.5 dB for the remaining trials. ILDs could not be higher than 20 dB or lower than 0 dB. If a listener had four incorrect responses at 20-dB ILD, the track was terminated immediately and the ILD threshold was recorded as 20 dB. This happened three times, once for one ONH listener and twice for another ONH listener. The arithmetic mean over the ILD values for the last 10 reversals of the adaptive track was used to calculate the left-right lateralization discrimination threshold per track.

Five target frequencies (f_{tar} = 0.5, 1, 2, 4, and 8 kHz) and five interferer frequencies (f_{int} = 0.5, 1, 2, 4, and 8 kHz) were tested. Control conditions tested the target frequencies in isolation. The across-frequency binaural interference conditions tested the target frequencies in the presence of a diotic (zero ITD and zero ILD) interferer, and every possible combination of the target and interferer frequencies was tested with the exception that the target and interference frequency could not be the same. At least three ILD thresholds were measured for each condition. This resulted in a total of 75 blocks in the experiment [5 f_{tar} × 5 f_{int} (including a no interferer control condition) × 3 blocks]. For one YNH listener who had more variability in their individual ILD thresholds, six thresholds were measured per condition because they had the time to do so. The order of conditions was randomized across the listeners and each condition was tested once before any condition was repeated, which helped minimize any order effects. Testing was ∼6 h per listener, usually tested in 1- or 2-h sessions that occurred on 3–4 different days. Most listeners finished the study within 15 days, and one finished in 25 days. The procedure was the same as experiment 1 of Rosen and Goupell (2022).

Analysis

Inferential statistics were performed using R version 4.0.3 (R Development Core Team, 2021). The *buildmer* (v2.3) (Voeten, 2020) and *lme4* (v1.1–26) (Bates et al., 2015) packages were used.

The first analysis was a linear mixed-effect model, which was performed for the single-frequency ILD discrimination thresholds and random intercepts were included for each listener. The dependent variable was the ILD discrimination threshold (in dB), where thresholds from the individual tracks were included to predict the average (i.e., listeners had at least three repeated measurements per condition). The independent categorical variables were age [2 levels: YNH (reference) and ONH] and frequency [f_{tar}, 5 levels: 0.5, 1, 2, 4, and 8 kHz (reference)]. The rationale for using 8 kHz as the reference was that the greatest variation in hearing thresholds were at that frequency (**Figure 1**). An independent continuous variable, the interaural average of the hearing threshold (θ_{tar}), was included as a frequency-specific predictor.

The second analysis started as a linear mixed-effect model, which was performed on the difference of the ILD thresholds in dB between conditions with no interferer and those with an interferer, called the binaural interference index (Bibee and Stecker, 2016). Random intercepts were included for each listener. The model building process with *buildmer*, which only includes terms that significantly improve the model, found that the random listener intercepts did not meet this requirement. Therefore, this analysis was reduced to a multiple regression. This analysis also used thresholds for individual tracks to predict performance. The independent categorical variables were age [2 levels: YNH (reference) and ONH], target frequency [f_{tar}, 5 levels: 0.5, 1, 2, 4, and 8 kHz (reference)], and interferer frequency [f_{int}, 5 levels: 0.5, 1, 2, 4, and 8 kHz (reference)]. Independent continuous variables included the interaural average hearing thresholds for the target (θ_{tar}) and interferer (θ_{int}) frequencies.

RESULTS

Single-Tone ILD Discrimination Thresholds

Figure 2 shows the average ILD thresholds for the conditions for the single tones (i.e., there was no diotic interferer at a remote frequency). The results of the linear mixed-effect model are reported in **Table 1**. The ONH listeners had significantly higher thresholds than YNH listeners ($p = 0.020$; **Figure 2A**), but there were no significant interactions with age. ILD thresholds increased with increasing θ_{tar} ($p = 0.004$; **Figure 2B**). The correlation between age and θ_{tar} was $r = -0.23$, suggesting that these were fairly independent effects for the listeners tested in this study. There was also a significant main effect of frequency, where worse ILD thresholds occurred at 1 kHz compared to 8 kHz ($p = 0.001$).

Across-Frequency Binaural Interference

Figure 3 shows ILDs thresholds for the target-interferer pairs as a function of target and interferer frequency. The thresholds for the ONH listeners were generally higher than the thresholds for the YNH listener.

To better understand the age-related and frequency-specific changes to the across-frequency binaural processing, **Figure 4** shows the across-frequency binaural interference index (the difference between the target-interferer pair threshold and the target only threshold in dB from **Figure 3**) organized as a grid of target and interferer frequencies. The effects of frequency have some similar trends for the two age groups (e.g., f_{tar} = 1 kHz or f_{int} = 2 kHz), but there were also notable differences (e.g., f_{tar} = 0.5 kHz, f_{int} = 0.5 kHz, or f_{int} = 1 kHz).

The results of the multiple linear regression are shown in **Table 2**. The most important result from this analysis was that, depending on the frequency combination, the binaural interference index was larger for ONH listeners. **Table 2** demonstrates numerous higher-order interactions with age, target frequency, and interferer frequency. These significant

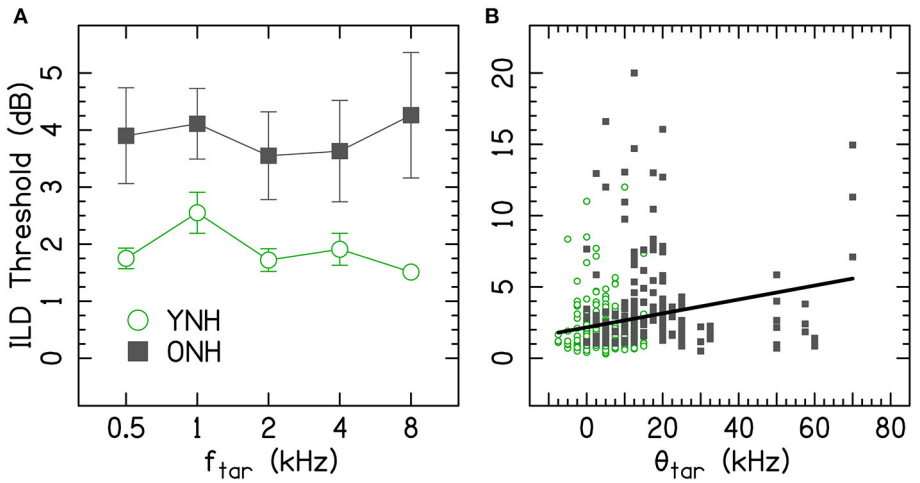

FIGURE 2 | (A) Average ILD thresholds for single tones. Error bars represent ±1 standard error of the listener mean. **(B)** Individual ILD thresholds for single tones as a function of hearing threshold (θ_{tar}). f_{tar}, target frequency; ONH, older normal hearing; YNH, younger normal hearing; θ_{tar}, average interaural hearing threshold at the target frequency. The YNH data have been previously reported. Reproduced from Beth Rosen and Matthew J. Goupell, "The effect of target and interferer frequency on across-frequency binaural interference of interaural-level-difference sensitivity," J. Acoust. Soc. Am. 151, 924–938 (2022), https://aip.scitation.org/doi/10.1121/10.0009398, with the permission of Acoustical Society of America.

TABLE 1 | Results of the linear mixed-effect model for the ILD thresholds for single tones.

Fixed effects	Estimate	SE	df	t	*p*	
Intercept	**1.431**	**0.418**	**47.0**	**3.43**	**0.001**	**
Age(ONH)	**1.555**	**0.636**	**32.1**	**2.44**	**0.020**	*
θ_{tar}	**0.032**	**0.011**	**467.7**	**2.91**	**0.004**	**
f_{tar}(0.5 kHz)	0.290	0.271	445.5	1.07	0.286	
f_{tar}(1 kHz)	**0.889**	**0.275**	**446.3**	**3.23**	**0.001**	**
f_{tar}(2 kHz)	0.190	0.277	446.7	0.69	0.492	
f_{tar}(4 kHz)	0.220	0.269	445.1	0.82	0.414	
Random effects	Variance	SD				
Listener (intercept)	2.50	1.58				
Residual	3.35	1.83				

Rows in bold highlight significant effects. Significance levels: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. df, degrees of freedom; f_{tar}, target frequency; ONH, older normal hearing; SD, standard deviation; SE, standard error; θ_{tar}, average interaural hearing threshold at the target frequency.

interactions support the hypothesis that across-frequency ILD processing changes with age, and that it changes in a frequency-specific manner.

There were the numerous significant four-way interactions that were difficult to fully interpret together in **Table 2**. Therefore, some of the four-way interactions and some of the more obvious lower-order interactions from the **Figure 4** that include the factor age will be highlighted. When examining the columns of **Figure 4**, there were relatively larger binaural interference indices for ONH listeners at $f_{tar} = 2$ kHz [Age(ONH)×θ_{int}×f_{tar}(2 kHz), $p = 0.024$] and $f_{tar} = 4$ kHz [Age(ONH)×θ_{int}×f_{tar}(4 kHz), $p = 0.004$]. When examining the rows of **Figure 4**, there were larger binaural interference indices for ONH listeners at $f_{int} = 0.5$ [Age(ONH)×θ_{tar}×f_{int}(0.5 kHz), $p = 0.016$], 1 kHz [Age(ONH)×θ_{tar}×f_{int}(1 kHz), $p = 0.002$], and 2 kHz [Age(ONH)×θ_{tar}×f_{int}(2 kHz), $p = 0.001$]. There were smaller binaural interference indices for ONH listeners at $f_{int} = 4$ kHz [Age(ONH)×θ_{tar}×f_{int}(4 kHz), $p = 0.016$]. In addition, there were significant four-way interactions that depended on the target and interferer thresholds θ_{tar} and θ_{int}, suggesting both play a role in the amount of across-frequency interference that occurred.

DISCUSSION

Aging and hearing loss affect spatial-hearing performance, but little is understood about age-related changes to across-frequency binaural processing and its frequency dependence. Binaural processing requires temporal precision, which degrades with increasing age. Using an across-frequency binaural interference task, where remote diotic (i.e., zero ILD and ITD) interferers

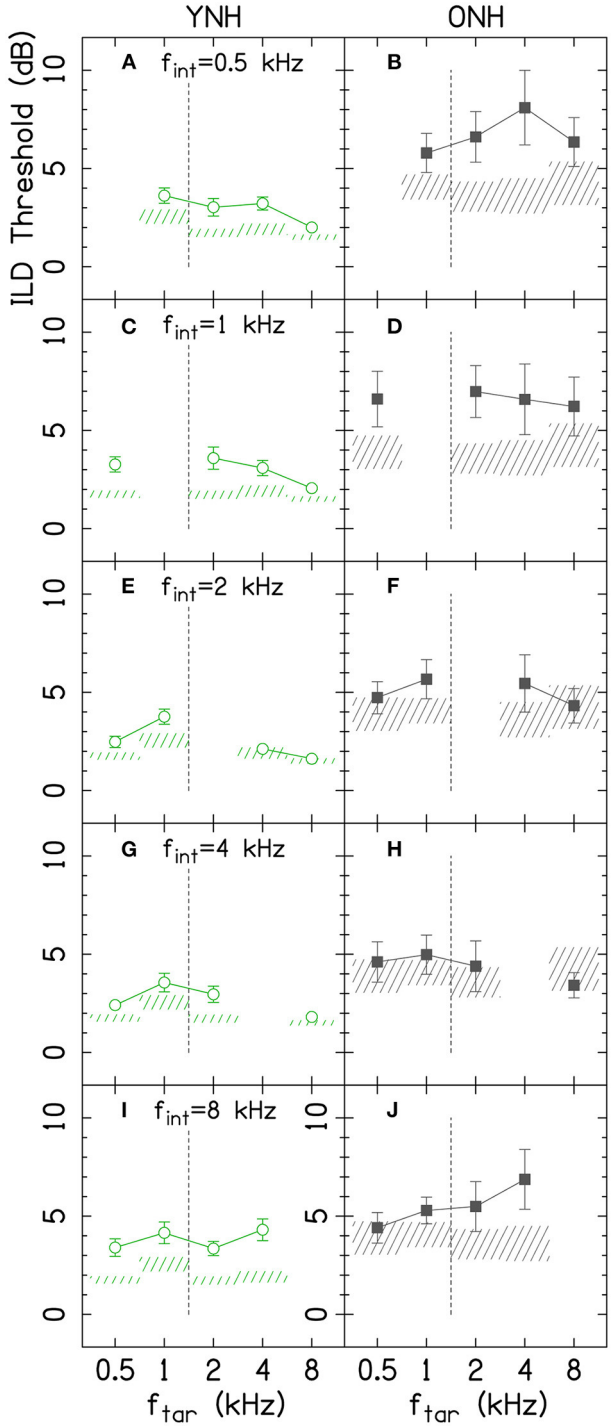

FIGURE 3 | Average ILD discrimination thresholds for target-interferer pairs are shown by data points for YNH (left column) and ONH (right column) listeners. Different rows represent different f[^{int}]. Error bars on each point represent ±1 standard error of the listener mean. The shaded areas represent the average ±1 standard error for the single-tone conditions, which were copied from **Figure 2**. The vertical dashed lines show the border where low-frequency ITDs are particularly potent. f_{int}, interferer frequency; f_{tar}, target frequency; ONH, older normal hearing; YNH, younger normal hearing. The YNH data have been previously reported. Reproduced from Beth Rosen and

(Continued)

FIGURE 3 | Matthew J. Goupell, "The effect of target and interferer frequency on across-frequency binaural interference of interaural-level-difference sensitivity," J. Acoust. Soc. Am. 151, 924–938 (2022), https://aip.scitation.org/doi/10.1121/10.0009398, with the permission of Acoustical Society of America.

often cause elevated target thresholds, ILD discrimination thresholds were measured as a function of target and interferer frequency in younger and older adult listeners, all having normal hearing thresholds up to 2 kHz. Across-frequency ILD processing shows relatively large effects of frequency compared to single tones (Goupell and Stakhovskaya, 2018a), but not the extreme asymmetry seen for ITD processing (Heller and Richards, 2010). The older listeners had relatively good hearing for their age, many with normal to near-normal thresholds, and increasing variability at 4 and 8 kHz where some had larger losses; nonetheless, they still had worse hearing threshold than their younger counterparts (**Figure 1**). It was hypothesized that aging would reduce binaural sensitivity and increase across-frequency binaural interference at all frequencies because of central changes, such as non-frequency-specific age-related temporal processing deficits. In addition, it was hypothesized that there would be relatively more interference caused by the lower frequency (e.g., <4 kHz) interferers because of the onset of age-related high-frequency hearing loss. These hypotheses were supported to some extent (**Figures 3**, **4**; **Table 2**).

Single-Tone ILD Discrimination Thresholds

The ILD discrimination thresholds for the single tones (i.e., the control conditions) were 3.9 dB on average for the ONH listeners, which was significantly higher than the 1.9 dB for the YNH listeners (**Figure 2**, **Table 1**). The significant increase in ILD discrimination thresholds for the ONH compared to the YNH listeners of the current study is larger than some other reports. For example, Herman et al. (1977) tested eight younger and eight older listeners with audiometrically normal hearing up to 2 kHz, and presented the listeners broadband clicks. They found no significant difference in ILD discrimination thresholds, the average threshold was 1.4 dB for the younger listeners and 1.5 dB for the older listeners. Babkoff et al. (2002) tested 78 listeners that had a range of ages from 22 to 88 yrs, had audiometrically normal hearing up to 2 kHz, and presented listeners broadband click trains. They also found no significant effects of age on intracranial lateralization and discrimination thresholds for ILDs.

Several studies have compared ILD discrimination thresholds for normal-hearing vs. hearing-impaired listeners, with some of the hearing-impaired listeners being older in age. These studies used narrowband noises (1/3rd-octave bandwidth), and include Gabriel et al. (1992; 2 of 4 hearing-impaired listeners >60 yrs), Koehnke et al. (1995; 2 of 11 hearing-impaired listeners >60 yrs), Smith-Olinde et al. (2004; some of 6 hearing-impaired listeners >60 yrs), and Spencer et al. (2016; 1 of 10 hearing-impaired listeners >60 yrs). In these studies, there was a small increase or no significant effect of hearing impairment on ILD thresholds.

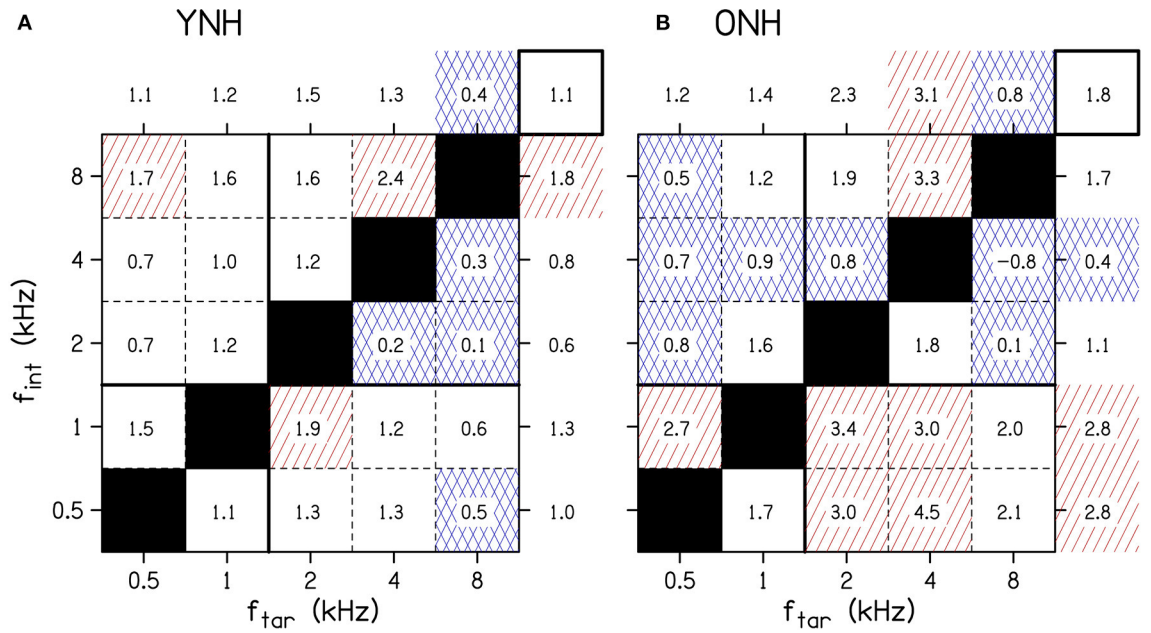

FIGURE 4 | The average amount of binaural interference for YNH **(A)** and ONH **(B)** listeners. The numbers in the boxes represent the binaural interference index for target and interferer frequency combinations in dB. The numbers outside of the main grid are the average of each column and row. The overall average interference across all conditions is shown by the number in the top right box of each panel. Cells highlighted by red diagonal lines denote a relatively large amount of binaural interference, defined as at least 50% greater than the overall average. Cells highlighted by blue crossed lines denote a relatively small amount of binaural interference, defined as at least 50% less than average. The solid horizontal and vertical lines between 1 and 2 kHz show the border where low-frequency ITDs are particularly potent. f_{int}, interferer frequency; f_{tar}, target frequency; ONH, older normal hearing; YNH, younger normal hearing. The YNH data have been previously reported. Reproduced from Beth Rosen and Matthew J. Goupell, "The effect of target and interferer frequency on across-frequency binaural interference of interaural-level-difference sensitivity," J. Acoust. Soc. Am. 151, 924–938 (2022), https://aip.scitation.org/doi/10.1121/10.0009398, with the permission of Acoustical Society of America.

Therefore, the effect of age in the current study appears to be relatively larger than other similar studies.

One difference that might reconcile the different aging effects across studies is the stimuli that were used. The current study found a factor of two increase in ILD discrimination thresholds between age groups and used pure tones (a single frequency); the other studies found smaller or no increases and used wider bandwidth noise or click stimuli. Other studies have noted improved ILD and ITD performance with increasing stimulus bandwidth (Hartmann and Constan, 2002; Best and Swaminathan, 2019). In addition, ILD discrimination thresholds are worse for steady-state stimuli (like the tones used in the present study) compared to modulated stimuli (like noises) (Laback et al., 2017; Rosen and Goupell, 2022). Discrepancies in aging effects across studies such as for sound-localization performance (Dobreva et al., 2011; Otte et al., 2013) may also be related to differences in stimuli.

It is also possible to reconcile this relatively large perceptual result using tones in the current study with physiological findings. The relatively large aging effects could be a result of stronger neural adaptation for steady-state compared to modulated stimuli in older compared to younger listeners (Devries et al., 2022). Since physiological evidence for such age-related changes to the lateral superior olivary complex appear small (Casey, 1990; Finlayson and Caspary, 1993; Finlayson, 1995), such proposed changes may occur at higher centers (Laumen et al., 2016; Ashida et al., 2021).

Besides the age-related increase in ILD thresholds, there was a significant single-channel ILD frequency dependence, where 1 kHz had higher ILD thresholds than 8 kHz (**Figure 2**, **Table 1**). Other studies have also reported higher thresholds at 1 kHz in YNH listeners (Mills, 1960; Grantham, 1984; Yost and Dye, 1988; Goupell and Stakhovskaya, 2018a; Brown and Tollin, 2021; Rosen and Goupell, 2022); the reason for this increase may be a result of the interaction of a zero ITD cue on the ILD information (Brown and Tollin, 2021). There were no significant interactions between age and frequency to suggest the relative insensitivity at 1 kHz changes with age, although the frequency resolution of the current study may not have been appropriate to observe such a change. Any ILD frequency dependence has yet to be reconciled with neurophysiological recordings, which reveal little frequency dependence in lateral superior olivary neurons (Jones et al., 2015).

It is unclear why there is such a small ILD frequency dependence; some additional information from the present study contributes to better understanding this phenomenon. The average interaural hearing threshold was included as a frequency-specific predictor in the statistical model. The results in **Table 1** revealed that ILD thresholds increased with increasing θ_{tar}. The effect of average hearing threshold is perhaps unsurprising,

TABLE 2 | Main effects and significant interactions of the multiple regression for the binaural interference index (interactions that were not significant were omitted for clarity).

Fixed main effects	Estimate	SE	t	*p*	
Intercept	**3.190**	**0.834**	**3.825**	**0.0001**	***
Age(ONH)	−5.691	3.019	−1.885	0.060	
θ_{tar}	−0.055	0.120	−0.461	0.645	
θ_{int}	−0.154	0.134	−1.148	0.251	
f_{tar}(0.5 kHz)	0.309	1.115	0.277	0.782	
f_{tar}(1 kHz)	−0.929	1.065	−0.873	0.383	
f_{tar}(2 kHz)	−0.686	0.977	−0.703	0.482	
f_{tar}(4 kHz)	0.102	0.706	0.144	0.886	
f_{int}(0.5 kHz)	**−2.783**	**1.115**	**−2.495**	**0.013**	*
f_{int}(1 kHz)	**−2.723**	**1.065**	**−2.558**	**0.011**	*
f_{int}(2 kHz)	**−2.728**	**0.639**	**−4.268**	**<0.0001**	***
f_{int}(4 kHz)	**−2.708**	**0.935**	**−2.897**	**0.004**	**
Interactions					
f_{tar}(2 kHz) × f_{int}(1 kHz)	**3.541**	**1.368**	**2.589**	**0.010**	**
Age(ONH) × θ_{tar}	**0.495**	**0.155**	**3.200**	**0.001**	**
Age(ONH) × θ_{int}	**0.573**	**0.246**	**2.328**	**0.020**	*
Age(ONH) × f_{tar}(2 kHz)	**7.871**	**3.499**	**2.250**	**0.025**	*
Age(ONH) × f_{tar}(4 kHz)	**5.633**	**2.536**	**2.221**	**0.026**	*
Age(ONH) × θ_{tar} × θ_{int}	**−0.014**	**0.005**	**−2.783**	**0.005**	**
Age(ONH) × θ_{tar} × f_{tar}(2 kHz)	**−0.480**	**0.214**	**−2.236**	**0.025**	*
Age(ONH) × θ_{tar} × f_{int}(0.5 kHz)	**−0.399**	**0.165**	**−2.414**	**0.016**	*
Age(ONH) × θ_{tar} × f_{int}(1 kHz)	**−0.504**	**0.166**	**−3.044**	**0.002**	**
Age(ONH) × θ_{tar} × f_{int}(2 kHz)	**−0.450**	**0.136**	**−3.323**	**0.001**	***
Age(ONH) × θ_{tar} × f_{int}(4 kHz)	**−0.420**	**0.174**	**−2.414**	**0.016**	*
Age(ONH) × θ_{int} × f_{tar}(2 kHz)	**−0.575**	**0.254**	**−2.263**	**0.024**	*
Age(ONH) × θ_{int} × f_{tar}(4 kHz)	**−0.662**	**0.230**	**−2.875**	**0.004**	**
Age(ONH) × θ_{int} × f_{int}(2 kHz)	**−0.386**	**0.193**	**−2.003**	**0.045**	*
Age(ONH) × f_{tar}(1 kHz) × f_{int}(2 kHz)	**−8.688**	**3.446**	**−2.522**	**0.012**	*
Age(ONH) × f_{tar}(2 kHz) × f_{int}(0.5 kHz)	**−9.750**	**4.206**	**−2.318**	**0.021**	*
Age(ONH) × f_{tar}(4 kHz) × f_{int}(0.5 kHz)	**−11.903**	**3.802**	**−3.131**	**0.002**	**
Age(ONH) × θ_{tar} × f_{tar}(1 kHz) × f_{int}(0.5 kHz)	**0.866**	**0.291**	**2.973**	**0.003**	**
Age(ONH) × θ_{tar} × f_{tar}(1 kHz) × f_{int}(2 kHz)	**0.914**	**0.287**	**3.191**	**0.001**	**
Age(ONH) × θ_{tar} × f_{tar}(1 kHz) × f_{int}(4 kHz)	**0.926**	**0.308**	**3.003**	**0.003**	**
Age(ONH) × θ_{tar} × f_{tar}(2 kHz) × f_{int}(0.5 kHz)	**1.040**	**0.285**	**3.646**	**0.0003**	***
Age(ONH) × θ_{tar} × f_{tar}(2 kHz) × f_{int}(4 kHz)	**0.729**	**0.288**	**2.530**	**0.011**	*
Age(ONH) × θ_{tar} × f_{tar}(4 kHz) × f_{int}(0.5 kHz)	**0.375**	**0.157**	**2.387**	**0.017**	*
Age(ONH) × θ_{int} × f_{tar}(0.5 kHz) × f_{int}(1 kHz)	**0.776**	**0.349**	**2.226**	**0.026**	*
Age(ONH) × θ_{int} × f_{tar}(2 kHz) × f_{int}(1 kHz)	**0.844**	**0.358**	**2.356**	**0.019**	*
Age(ONH) × θ_{int} × f_{tar}(4 kHz) × f_{int}(0.5 kHz)	**0.999**	**0.329**	**3.034**	**0.002**	**
θ_{tar} × θ_{int} × f_{tar}(0.5 kHz)	**0.022**	**0.008**	**2.645**	**0.008**	**
θ_{tar} × θ_{int} × f_{tar}(1 kHz)	**0.021**	**0.009**	**2.480**	**0.013**	*
θ_{tar} × θ_{int} × f_{tar}(2 kHz)	**0.031**	**0.009**	**3.553**	**0.0004**	***
θ_{tar} × θ_{int} × f_{tar}(4 kHz)	**0.027**	**0.007**	**3.661**	**0.0003**	***
θ_{tar} × θ_{int} × f_{int}(1 kHz)	**0.030**	**0.009**	**3.491**	**0.0005**	***
θ_{tar} × θ_{int} × f_{int}(2 kHz)	**0.024**	**0.006**	**3.876**	**0.0001**	***
θ_{tar} × θ_{int} × f_{int}(4 kHz)	**0.021**	**0.008**	**2.607**	**0.009**	**
θ_{tar} × θ_{int} × f_{tar}(0.5 kHz) × f_{int}(4 kHz)	**−0.030**	**0.012**	**−2.572**	**0.010**	*
θ_{tar} × θ_{int} × f_{tar}(1 kHz) × f_{int}(0.5 kHz)	**−0.044**	**0.019**	**−2.334**	**0.020**	*
θ_{tar} × θ_{int} × f_{tar}(1 kHz) × f_{int}(2 kHz)	**−0.041**	**0.014**	**−2.881**	**0.004**	**
θ_{tar} × θ_{int} × f_{tar}(1 kHz) × f_{int}(4 kHz)	**−0.033**	**0.010**	**−3.190**	**0.001**	**
θ_{tar} × θ_{int} × f_{tar}(2 kHz) × f_{int}(0.5 kHz)	**−0.044**	**0.014**	**−3.086**	**0.002**	**
θ_{tar} × θ_{int} × f_{tar}(2 kHz) × f_{int}(4 kHz)	**−0.040**	**0.011**	**−3.675**	**0.0002**	***
θ_{tar} × θ_{int} × f_{tar}(4 kHz) × f_{int}(0.5 kHz)	**−0.042**	**0.011**	**−3.760**	**0.0002**	***

Rows in bold highlight significant effects. Significance levels: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. f_{int}, interferer frequency; f_{tar}, target frequency; ONH, older normal hearing; SD, standard deviation; SE, standard error; θ_{int}, average interaural hearing threshold at the interferer frequency; θ_{tar}, average interaural hearing threshold at the target frequency.

given the numerous studies suggesting the need to control for differences in stimulation level in studies investigating aging and hearing loss (e.g., Durlach et al., 1981; Häusler et al., 1983; Smith-Olinde et al., 2004; Gallun et al., 2021). What is slightly more surprising is that the younger listeners had typical hearing thresholds and the older listeners had relatively good hearing for their age, with elevated hearing thresholds at only 4 and 8 kHz. Some reports have shown that audiometric thresholds are not a significant predictor of binaural performance (e.g., Gabriel et al., 1992; Koehnke et al., 1995), but they did not utilize statistical approaches that were well-suited to include frequency-specific hearing thresholds as a predictor. Many previous studies had too few listeners to test for correlations between hearing thresholds and binaural performance, although it is sometimes possible to observe elevated hearing thresholds to correlate with worse binaural performance. For example, Spencer et al. (2016) found a significant correlation between hearing thresholds and ILD thresholds at 4 kHz for normal-hearing listeners, but not at 0.5 kHz for normal-hearing listeners, not for hearing-impaired listeners, and not for other binaural processing measures like ITD and interaural correlation change discrimination sensitivity. On the other hand, even small increases in hearing thresholds within an audiometrically normal hearing range appear to diminish binaural sensitivity (Bernstein and Trahiotis, 2016, 2018) and alter across-frequency binaural interference patterns (Bernstein and Trahiotis, 2021).

In summary, based on the current study, it appears that the individual variation in single-channel ILD thresholds are attributed to both age and hearing sensitivity. Future studies could investigate this more thoroughly by intentionally recruiting listeners with a wide range of average hearing sensitivity and hearing asymmetry, and using statistical approaches like mixed-effect models to appropriately handle frequency-specific predictors of performance.

Across-Frequency Binaural Interference

ILD thresholds increased in the presence of the interferer (**Figure 3**, compare points and shaded areas) and that amount changes depending on the target and interferer frequency. The amount of interference is most easily seen in **Figure 4**. The binaural interference indices were about twice as large for the older listeners (1.8 dB) compared to the younger listeners (1.1 dB; top-right corner box of each panel in **Figure 4**), which was not a significant increase [main effect of Age, $p = 0.060$; **Table 2**]. There were numerous higher-order interactions with age highlighting that the increases were specific to certain combinations of target and interferer frequencies.

To summarize the results for the younger listeners (**Figure 4A**), the least interference was experienced by the 8-kHz target tones and the most interference was produced by the 8-kHz interferer tones (see Rosen and Goupell, 2022 for a detailed summary). The amount of interference was not particularly well-predicted by the single-tone ILD thresholds. Much like the frequency dependence of the single-channel ILD thresholds, the frequency dependence for across-frequency binaural interference for ILDs currently has few compelling explanations (Rosen and Goupell, 2022).

The summary of the results for the older listeners is best understood in comparison to the younger listeners. Interferers at 0.5 and 1 kHz consistently had larger amounts of interference for the older listeners compared to the younger listeners (**Figure 4**, bottom two rows, below the solid line, highlighted by the number of boxes with red shading). Interferers at 2, 4, and 8 kHz had relatively smaller amounts of interference for the older listeners, which had smaller or comparable interference values compared to younger listeners (**Figure 4**, top three rows, above the solid line, highlighted by the number of boxes with blue shading). The boundary between 1 and 2 kHz is important to consider because the zero ITD of the stimuli may become particularly salient and important for stimuli <1.5 kHz. The binaural interference indices were the largest in the area that included the 0.5-, 1-, and 2-kHz interferer frequencies and the 2- and 4-kHz target frequencies (see **Figure 4B**, cluster of boxes with red diagonal lines). Since the binaural interference indices for the 4- and 8-kHz interferer frequencies were reduced for the older listeners compared to the younger listeners, this was consistent with the hypothesis about the relatively increasing importance of lower frequencies for older listeners, from either temporal processing deficits or hearing thresholds. Considering naturally occurring stimuli like speech, increasing the relative importance of lower-frequency ILDs could have some similarities to conditions in the present study; naturally occurring ILDs will trend toward zero in the low-frequency limit. This may be evidence for frequency-dependent plasticity to accommodate the aging auditory system. There were also significant interactions between age, target hearing thresholds, and interferer hearing thresholds, suggesting that the hearing thresholds at both the target and interferer frequencies contribute to the amount of interference.

Smith-Olinde et al. (1998) measured across-frequency binaural interference for three YNH (age range = 23–36 yrs) and six hearing-impaired (age range = 32–64 yrs) listeners using 1/3rd-octave narrowband noises centered at 0.5 and 4 kHz. Comparing the YNH listeners for the 0.5-kHz target and 4-kHz interferer, there was a 0.8-dB binaural interference index in that study and 0.7-dB binaural interference index in the current study (**Figure 4**), which is good correspondence. Comparing the YNH listeners for the 4-kHz target and 0.5-kHz interferer, there was a 0-dB binaural interference index in that study and a 0.7-dB binaural interference index in the current study. Comparing the hearing-impaired and ONH listeners for the 0.5-kHz target and 4-kHz interferer, there was a 0.2-dB binaural interference index in that study and 1.2-dB binaural interference index in the current study (**Figure 4**). Comparing the hearing-impaired and ONH listeners for the 4-kHz target and 0.5-kHz interferer, there was a 2.3-dB binaural interference index in that study and a 4.5-dB binaural interference index in the current study. Therefore, the current study often demonstrated more across-frequency binaural interference than in Smith-Olinde et al. (1998). The differences across studies may have been caused by differences in the stimuli [narrowband noises vs. tones (current study)], differences in level roving range [10 vs. 20 dB (current study)], and that study had some younger listeners with more hearing loss whereas the current study recruited older listeners with minimal hearing loss.

Few studies have considered the frequency dependence of sound localization or lateralization for both ITD and ILDs, as well as any age- or hearing-loss-related changes to such frequency dependence (Eddins and Hall, 2010; Gallun et al., 2021). It is clear that YNH listeners heavily weight low-frequency ITDs for broadband sound localization (Wightman and Kistler, 1992; Macpherson and Middlebrooks, 2002), particularly around 600–700 Hz (Bilsen and Raatgever, 1973; Stern et al., 1988). There are contributions from both ITDs and ILDs to intracranial lateralization when investigating how ITDs and ILDs derived from natural stimuli affect lateralization (Goupell and Stakhovskaya, 2018b). The contributions of ILDs are relatively small at lower frequencies compared to higher frequencies, which is partially a result of ILDs being physically smaller at low frequencies and that ILDs applied to lower frequencies produce less lateralization than ILDs applied to higher frequencies (Bernstein and Trahiotis, 2011; Goupell and Stakhovskaya, 2018b). For the stimuli in the present study, the zero ITDs could contribute to the changes in lateralization across frequency. Nevertheless, ITD and ILD reweighting appears to be possible with explicit training. For example, Klingel et al. (2021) found that YNH listeners reweighted ITD or ILD cues using 3-kHz noise bursts and seven days of audio-visual training. Keating et al. (2014) showed ferrets improved their 1-kHz ILD discrimination thresholds with explicit training, but not their 2-kHz thresholds, and was discussed in terms of reweighting of ITD and ILD cues. Humans can also accommodate changes to their spatial maps in response to changes in ITDs and ILDs induced by ear plugs (Kumpik et al., 2010). It is unclear what physiological center combines ITD and ILD information, and it is also unclear where across-frequency processing occurs, but it is possible that these centers are quite high, even cortical, if they readily experience plasticity. Sollini et al. (2017) found across-frequency processing of ILDs in the auditory cortex that was absent in the inferior colliculus.

Finally, one noteworthy condition in **Figure 4B** for the older listeners was the 8-kHz target, 4-kHz interferer condition. This condition had a binaural interference index of −0.8 dB (SD = 2.3 dB), which is a condition that could be demonstrating facilitation (i.e., negative interference). This value was not statistically lower than 0 dB (one-sample two-tailed t-test, $p = 0.245$), and therefore was is not distinguishable from measurement noise. Hence, no measurement to date has provided convincing evidence of across-frequency ILD-based facilitation (Bernstein and Trahiotis, 1995).

Limitations and Future Directions

While the present study expands the understanding of the age-dependent frequency-dependent changes of across-frequency ILD processing, there are some clear future directions. First, as is done in many aging studies, older listeners with minimal hearing loss up to 2–4 kHz were recruited for the current study. Despite this, significant effects of hearing thresholds occurred in this current study, consistent with other reports showing even small changes in hearing thresholds affect binaural sensitivity (e.g., Bernstein and Trahiotis, 2016, 2018). An alternative approach would be to not limit the listener recruitment based on hearing thresholds or age (e.g., recruit younger listeners with hearing loss). Larger amounts of hearing loss and variability across frequency would help clarify the roles of hearing thresholds (i.e., assumed to be peripheral changes) and age (i.e., assumed to be central changes).

Given the effect of hearing thresholds, another future direction would be to systematically and parametrically investigate stimulus level effects. Smith-Olinde et al. (2004) measured across-frequency binaural interference for four YNH (age range = 27–39 yrs) and seven hearing-impaired listeners (age range = 40–66 yrs) at either equal sound pressure level or equal sensation level, compensating for the stimulus presentation level confound for the hearing-impaired listeners. Others have noted the importance of stimulus level in binaural perception tasks when testing hearing-impaired listeners (Häusler et al., 1983; Gallun et al., 2021). This is a clearly important variable for investigation, because across-frequency binaural interference studies have not systematically explored how the relative level across frequencies affects interference, despite how this should occur naturally in stimuli like speech and in listeners who have different configurations of hearing loss.

The frequency-specific average interaural hearing thresholds were significant predictive factors; the frequency-specific interaural difference in hearing thresholds (i.e., asymmetry) could be similarly considered. It was not possible to use this approach in the current study because there were mostly interaurally symmetric listeners. It is common in binaural-hearing studies to recruit interaurally symmetric listeners with $\leq$10 dB interaural hearing threshold difference. Interaural threshold asymmetry might induce plasticity that could be age dependent. Listeners with asymmetric hearing appear to perceive centered images with equal sound pressure levels presented to the two ears instead of equal sensation levels (Simon and Aleksandrovsky, 1997) and discrimination thresholds are often best at equal sound pressure levels (Hawkins and Wightman, 1980; Smoski and Trahiotis, 1986; Koehnke et al., 1995).

An across-frequency binaural interference paradigm was used in a highly controlled laboratory test, where some frequency bands have zero ITD and/or ILD. Natural sound sources away from the midline have combinations of non-zero ITDs and ILDs across frequencies. Future studies like Goupell and Stakhovskaya (2018b) that investigate age- and hearing-loss-related changes to lateralization or localization using interaural differences derived from natural stimuli would be another important future direction.

The current data could be interpreted as evidence for frequency-dependent plasticity as a listener ages. Another approach of assessing age-related plasticity would be to measure across-frequency binaural interference longitudinally so that the age-related and frequency-dependent differences in binaural interference are confirmed within the same listeners. There is a possibility that these patterns are partially a result of idiosyncratic listener tendencies, a hallmark of across-frequency binaural interference studies (Best et al., 2007, 2021), from a small set of listeners. Another alternative interpretation of the data is that older listeners have difficulty inhibiting distracting stimuli (Hasher et al., 1991). The physiological center where

across-frequency binaural interference occurs is unknown, but given that release from interference that occurs when using grouping and streaming paradigms (Best et al., 2007), this suggests a higher (perhaps cortical) level, which would be amenable to a non-auditory cognitive explanation. An argument against a non-auditory age-related cognitive change is that there would be little reason to include frequency-dependent changes with age.

CONCLUSIONS

The frequency dependence of across-frequency binaural interference was compared across younger and older listeners, all listeners having relatively good hearing thresholds for their age, but the older listeners had larger average audiometric thresholds compared to the younger listeners. ILD thresholds were worse for older compared to younger listeners and the amount of interference at specific target-interferer frequency combinations also increased. Frequency-specific hearing thresholds also contributed to the increased ILD thresholds and amount of interference. This provides some evidence for plasticity in the frequency weighting of binaural information.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://doi.org/10.17605/OSF.IO/AF8M3.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board in the Division of Research. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG obtained funding for the study, designed the study, programmed the experiment, oversaw data collection, analyzed the data, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Effect of hearing loss on cognitive function in patients with mild cognitive impairment: A prospective, randomized, and controlled study

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Background: Hearing loss (HL) may increase the risk of cognitive decline in the elderly. However, the randomized controlled study on the effect of HL on cognitive function in mild cognitive impairment (MCI) is very limited.

Methods: From 1 November 2020 to 30 March 2022, 1,987 individuals aged 55–65 years were randomly divided into the MCI with hearing impairment (MCI-HI), MCI without HI (MCI-nHI), and no MCI (nMCI) groups by stratified sampling, with 30 participants in each group. The Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the pure tone audiometry (PTA), and the auditory brainstem response (ABR) were measured at baseline and a follow-up 12 months later. The trial protocol was registered with ClinicalTrials.gov with the registration number NCT05336942.

Results: Among the 90 participants, the average age was 60.41 ± 6.48 years. In the MCI-HI group at baseline, the PTA score of both the ears was negatively correlated with the naming and memory score ($p < 0.05$), and the PTA score of both the ears was negatively correlated with the MoCA and abstraction score at the 12-month follow-up ($p < 0.05$). However, there were no significant differences among the PTA, the ABR, the MMSE, and the MoCA scores in the MCI-nHI and nMCI groups ($p > 0.05$). Regression analysis showed that the PTA score of the right ear at baseline was an important factor associated with the MoCA, visuospatial/executive, naming, and abstraction scores at the 12-month follow-up ($\beta = -0.776$ to -0.422, $p < 0.05$).

Conclusion: HL was significantly negatively associated with cognitive function only in patients with MCI with hearing impairment (HI), and the PTA of the right ear may be a predictor of cognitive decline after 1 year in patients with MCI with HI. This information may help primary healthcare clinicians to prevent MCI by screening and intervening in care for elderly patients with HL.

KEYWORDS

hearing loss, cognitive function, mild cognitive impairment, MCI, HL

Background

More than 55 million people worldwide suffer from dementia, and this number is expected to increase to ∼78 million affected people in 2030, with an estimated cost of US $2 trillion by 2050 (Jia et al., 2020; Gauthier et al., 2021). Mild cognitive impairment (MCI) is a symptomatic precursor stage of cognitive decline, and an intermediate state between dementia and normal cognitive function (Hill et al., 2017; Jongsiriyanyong and Limpawattana, 2018; Hemminghyth et al., 2020). The risk of Alzheimer's disease in patients with MCI is 10 times that of people with normal cognitive function, and MCI has become the most important risk factor for dementia (Serrano-Pozo and Growdon, 2019; Scheltens et al., 2021). A systematic review showed that the conversion rates from MCI to vascular dementia, Alzheimer's disease, and dementia were 6.2, 33.6, and 39.2%, respectively (Mitchell and Shiri-Feshki, 2009). Identifying modifiable risk factors for MCI will enable early intervention to prevent or substantially delay the onset of dementia (Vega and Newhouse, 2014; Sachs-Ericsson and Blazer, 2015).

The 2021 World Hearing Report shows that hearing loss (HL) affects more than 1.5 billion people worldwide, with more than 65% of those over 60 years of age having some degree of hearing loss (Chadha et al., 2021). Elderly people with hearing impairment (HI) are 2–5 times more likely to develop dementia than those with normal hearing (Griffiths et al., 2020). Most prospective cohort studies on the association between HL and Alzheimer's disease found that HL significantly increased the risk of Alzheimer's disease (Zheng et al., 2017; Llano et al., 2020, 2021). Some studies have also proposed age-related hearing loss (ARHL) as a possible non-invasive biomarker that predates the onset of clinical dementia by 5–10 years (Rutherford et al., 2018; Golub et al., 2019). Several potential mechanisms suggest that auditory deprivation may cause decreased socialization and affect cognitive function (Mick et al., 2014; Paciello et al., 2021). In addition, HL may cause cognitive resources to be diverted from memory function into auditory processing, which creates an excessive cognitive load on higher cortical functions (Pichora-Fuller et al., 2016; Van Canneyt et al., 2021).

However, few randomized controlled studies have focused on the effect of HL on MCI, and only a few cross-sectional studies have explored the association between HL and cognitive function. Lim and Loo (2018) conducted a cross-sectional study with a natural sample of 115 older adults and showed that HL is associated with MCI, but cognitive scoring may be confounded by poor hearing ability. The Mayo Clinic Study of Aging involving 4,812 participants found that participants with HL had a higher risk of MCI [hazard ratio (HR) 1.29, 95% CI 1.10–1.51], and considered that HL was associated with modestly greater cognitive decline (Vassilaki et al., 2019). Additionally, these studies did not separately describe left and right hearing functions in specific MCI samples. It is not known whether these differences relate to the link between HL and the risk of dementia. We attempted to use a community-based, multicenter natural sample to explore the long-term effects of left- and right-sided HL on cognitive function in patients with MCI by randomized, controlled, and longitudinal studies and compared the results with from normal hearing and normal cognitive populations. If a potential causal relationship between HL and MCI can be found, it will provide insights into the early prevention of cognitive impairment in clinical settings.

Methods

Study design

The study was designed as a prospective, randomized, and controlled survey. It is based on the Shanghai Pudong Mental Health Center (PMHC), Tongji University School of Medicine, which has been working on building a comprehensive cognitive impairment laboratory since 2008. Additionally, we cooperated with the hearing laboratory of Shanghai Punan Hospital in Pudong New District. The sample size of the study was calculated using the PASS version 21.0.3 (NCSS LLC, Utah, USA), a sample size, and power analysis software. The significance level was 0.05, a two-sided test was needed, and the power value was 0.8. The sample size of mild cognitive impairment with hearing impairment (MCI-HI), mild cognitive impairment without hearing impairment (MCI-nHI), and no mild cognitive impairment (nMCI) was estimated to be 27 participants per group. We set a 10% loss rate, including participants who could not complete the test or dropout due to special reasons, and finally determined a sample size of 30 participants for each group.

Participants and randomization procedure

Five of 23 communities were randomly selected in Pudong New District, Shanghai, from 1 November 2020 to 30 March 2022. A total of 1,987 individuals aged 55–65 years were selected from the cognitive function database of the communities. Among them, there were 225 patients with MCI and 1,696 individuals without cognitive impairment. A total of 201 patients with MCI were willing to undergo rapid hearing screening (Path Medical handheld hearing screeners) and patients or their guardians signed the consent form. By stratified sampling, patients were divided into the three groups: the MCI-HI group, the MCI-nHI group, and the nMCI group, with 30 participants in each group.

The following inclusion criteria were employed: (1) patients meeting the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (Roehr, 2013) diagnostic MCI; (2) 55 years old ≤ age ≤ 65 years old; (3) the Mini-Mental State Examination (MMSE) score ≤ 26 (Zhuang et al., 2021); (4) the pure tone audiometry (PTA) test score of the left or right ear ≥ 26 dB HL (Lapsley Miller et al., 2018); (5) normal or partially impaired ability to complete daily living activities; (6) ability to conduct verbal communication or written conversation; (7) capacity to complete the evaluation scale independently; and (8) participants or guardians agreed and signed the informed consent form for the study. The following exclusion criteria were employed: (1) patients meeting the DSM-5 (Roehr, 2013) diagnostic criteria of dementia, schizophrenia, neurosis, organic mental disorder, and intellectual disability; (2) severe extracranial trauma, limb disability, or physical illness; (3) those who were obviously blind or had difficulty in speech expression; (4) those who had perforated tympanic membrane perforation and used hearing aids previously; and (5) participants or guardians who did not sign the study informed consent or dropped out halfway.

Measures

Mini-mental state examination

The MMSE scale was proposed by Folstein et al. in 1975 (Folstein et al., 1975). It is widely used to measure cognitive impairment in clinical and research settings, including simple tasks in a number of areas: orientation, registration, attention, and calculation such as serial subtractions of seven, recall, and language. The Chinese version of the MMSE was created by Li et al. in 1989 and provides better reliability and validity. The Cronbach's α coefficient was 0.82 and the remeasuring reliability was 0.89 (Li et al., 1989). There are 30 items, with 1 point for the correctness and 0 points for error. Individuals with junior high school education and above had the MMSE ≤ 26, individuals with primary education had the MMSE ≤ 22, and individuals with no education had the MMSE ≤ 19, and were considered to have MCI (Zhang et al., 1999).

Montreal cognitive assessment

The MoCA scale was developed based on the clinical intuition of impairment commonly encountered in MCI and is best adapted to a screening test. This 30-point test, which was introduced by Nasreddine et al. in 2005 (Nasreddine et al., 2005), covers eight cognitive domains. The Chinese version of the MoCA was culturally and linguistically modified by Lu et al. in 2011. The Cronbach's α coefficient was 0.82, and the remeasuring reliability was 0.86 (Lu et al., 2011). There are 12 items, and the total score ranges from 0 to 30. The MoCA score > 26 indicates normal cognitive function. The cutoff value is 25, if the length of education is ≤ 12 years.

Pure tone audiometry

Pure tone audiometry testing is used to determine hearing threshold levels and to characterize the degree, and type of hearing loss. This test is a subjective and behavioral measurement of the hearing threshold (World Health Organization, 1999). The binaural (right ear first) air conductance hearing threshold was measured at 0.5, 1, 2, and 4 kHz. The average hearing threshold for normal hearing was defined as <25 dB HL (Louw et al., 2018).

Auditory brainstem response

Auditory brainstem response testing, which is also known as brainstem auditory evoked potentials (BAEPs), is the electrical response of the auditory nerve and brainstem nucleus caused by acoustic stimulation. This test can be used to express the electrical activities of the cochlea, auditory nerve, and brainstem auditory pathway and objectively evaluate the threshold of auditory behavior (Laumen et al., 2016). After receiving 10 ms of short sound stimulation, seven vertex positive waves with negative valleys can be traced from the surface of the skull skin. Wave V is generated in the auditory brainstem, which has the highest amplitude. This test is often used as a clinical diagnostic criterion for hearing loss (Møller and Jannetta, 1982). The binaural (right ear first) brainstem response threshold was measured at 0.5, 1, 2, and 4 kHz, which is usually 10–20 dB higher than that of pure tone audiometry (Eggermont, 2019; McKearney et al., 2021).

Procedure

With reference to the slopes of cognitive and hearing decline, all the enrolled participants received a cognitive function and hearing function at baseline and at a follow-up 12 months later (Kuo et al., 2021; Jang et al., 2022). Participants were instructed by an experimenter to assess the MMSE and the MoCA scales according to instructions in a quiet room, and to check the completion of each item. The evaluator has a Master's degree in psychiatry and is a registered cognitive function scale surveyor in China. Subsequently, we used the modern and versatile Eclipse platform produced by Interacoustics (Denmark), including a Melison AD104 diagnostic audiometer and AT235 automatic middle ear analyzer. Before the evaluation, the data and equipment of all the hearing test instruments were calibrated by the

manufacturer. The hearing test was carried out in a professional pure tone electric audiometry room, and the environmental requirements met the *Chinese Basic Audiometry of Pure Tone Air Conductance and Bone Conductance Threshold* (GB/T 16296-2018) (indoor noise level: $\leq$ 30 dB; air exchange rate: 10 times per h; indoor temperature: 20–26°C; and humidity: 40–80% RH) (CNSIPSP, 2018). The evaluation was performed by a senior otolaryngology specialist with a Chinese registered hearing test certificate. All the evaluators were trained for consistency.

Data analysis

Data were analyzed using the R Foundation for Statistical Computing (version 4.1.1) (R Software, 2021). We performed normality tests on all the data, using mean ± SD to statistically describe normal continuous data, median [interquartile range (IQR)] to statistically describe non-normal continuous data, and used the ANOVA or non-parametric rank-sum test for intergroup comparisons. For classified data, the frequency (percentage) was used for statistical description, and the chi-squared test/Fisher's exact probability method was used for intergroup comparison. Spearman's correlation analysis was used to evaluate the correlation between research indicators. Multiple linear regression analysis was performed to determine the association between hearing and cognitive functions. The difference was statistically significant at $p < 0.05$.

Ethics statement

The protocol for this research was approved by the Research Ethics Committee of the Shanghai Pudong New Area Mental Health Center and Tongji University School of Medicine (No: PDJWLL2019017). All the procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the

TABLE 1 Demographic characteristics of participants in each group.

Variable	Overall ($n = 90$)	MCI-HI ($n = 30$)	MCI-nHI ($n = 30$)	nMCI ($n = 30$)	$F/\chi 2$	p
Age in years, (mean ± SD)	60.41 ± 6.48	63.63 ± 4.29	61.27 ± 5.87	56.33 ± 6.86	12.49	<0.001**
Sex, *n* (%)					2.52	0.284
Male	40 (44.44%)	10 (33.33%)	14 (46.67%)	16 (53.33%)		
Female	50 (55.56%)	20 (66.67%)	16 (53.33%)	14 (46.67%)		
Education, *n* (%)					9.48	0.035*
Primary school and below	22 (24.44%)	11 (36.67%)	7 (23.33%)	4 (13.33%)		
Secondary school	62 (68.89%)	15 (50.00%)	23 (76.67%)	24 (80.00%)		
College and above	6 (6.67%)	4 (13.33%)	0 (0.00%)	2 (6.67%)		
Occupation, *n* (%)					5.63	0.160
incumbent or retired	59 (65.55%)	18 (60.40%)	18 (60.00%)	23 (76.67%)		
Unemployed	31 (34.45%)	12 (40.00%)	12 (40.00%)	7 (23.33%)		
Marital status, *n* (%)					3.76	0.450
Unmarried	16 (17.78%)	4 (13.33%)	4 (13.33%)	8 (26.67%)		
Married	68 (75.56%)	25 (83.33%)	24 (80.00%)	19 (63.33%)		
Divorced or widowhood	6 (6.67%)	1 (3.33%)	2 (6.67%)	3 (10.00%)		
Living condition, *n* (%)					2.13	0.230
Living alone	27 (30.00%)	7 (23.33%)	8 (26.67%)	12 (40.00%)		
Living with spouse or children	63 (70.00%)	23 (76.67%)	22 (73.33%)	18 (60.00%)		
Family financial satisfaction, *n* (%)					5.03	0.085
Satisfied	54 (60.00%)	16 (53.33%)	18 (60.00%)	20 (66.67%)		
Dissatisfied	36 (40.00%)	14 (46.67%)	12 (40.00%)	10 (33.33%)		
Self-rated health condition, *n* (%)					6.81	0.053
Good	23 (25.56%)	8 (26.67%)	6 (20.00%)	9 (30.00%)		
Ordinary	37 (41.11%)	10 (33.33%)	14 (46.67%)	13 (43.33%)		
Bad	30 (33.33%)	12 (40.00%)	10 (33.33%)	8 (26.67%)		

MCI-HI, Mild cognitive impairment with hearing impairment; MCI-nHI, Mild cognitive impairment without hearing impairment; nMCI, No mild cognitive impairment; *$p < 0.05$, **$p < 0.01$.

Declaration of Helsinki of 1975, as revised in 2008. The participants and guardians provided written informed consent to participate in this study. The trial protocol was registered with ClinicalTrials.gov with the registration number NCT05336942.

Results

Demographic characteristics

The demographic characteristics of participants from the MCI-HI, MCI-nHI, nMCI, and overall groups in terms of age, sex, education, occupation, marital status, living condition, family financial satisfaction, and self-rated health condition are shown in Table 1. Among the 90 participants, the average age was 60.41 ± 6.48 years, and the proportion of females was higher (55.56%) than males. In addition, most of the participants had a secondary school education (68.89%), were incumbent or retired (65.55%), were married (75.56%), lived with spouse or children (70.00%), were satisfied with family financial status (60.00%), and had ordinary self-rated health conditions (41.11%). There were significant differences in age and education among the three groups ($p < 0.05$), but there was no significant difference in other demographic variables ($p > 0.05$).

Hearing and cognitive functions

The hearing and cognitive functions among participants from the overall and the three groups at baseline and the 12-month follow-up are given in Table 2. Given the significant differences in age and education among the groups, after controlling for age and education as covariates, the differences in hearing and cognition functions among the groups were compared. In terms of hearing function, the PTA and ABR scores of the left and right ears were the highest in the MCI-HI group at baseline, and there were significant differences among the three groups ($p < 0.001$). Compared with the baseline, the PTA and ABR scores of both the ears increased in each group at the 12-month follow-up. However, there was no significant difference in the PTA scores in the MCI-HI group at the 12-month follow-up ($t = -1.51$ to 0.85, $p > 0.05$), while there were significant differences in the PTA and ABR scores in the other groups ($p < 0.05$). In terms of cognitive function, the MMSE and the MoCA scores in the nMCI group decreased at the 12-month follow-up, and there were significant differences ($z = -1.76$ to -0.94, $p < 0.01$). In the MCI-HI and MCI-nHI groups, the abstraction and memory scores of the MoCA decreased at the 12-month follow-up, and there were significant differences ($z = -5.06$ to -2.00, $p < 0.01$). There was no significant difference in the MMSE and the MoCA scores between the other groups ($p > 0.05$).

Correlation analysis

Spearman's correlation analysis was conducted on the PTA and ABR of the left and right ears, the MMSE, and eight dimensions of the MoCA among participants from the overall and three groups, as shown in Figure 1. In the MCI-HI group at baseline, the PTA score of both the ears was negatively correlated with the naming and memory scores ($p < 0.05$), and the ABR score of the right ear was negatively correlated with the MoCA and visuospatial/executive scores ($p < 0.05$). At the 12-month follow-up, the PTA scores of both the ears were negatively correlated with the MoCA and abstraction scores ($p < 0.05$). Meanwhile, the PTA scores of both the ears at baseline were negatively correlated with the MoCA scores at the 12-month follow-up ($p < 0.05$), and the ABR scores of the right ear at baseline were negatively correlated with the attention and language scores at the 12-month follow-up ($p < 0.05$). However, there were no significant differences between the PTA, ABR, the MMSE, and the MoCA scores in the MCI-nHI and nMCI groups ($p > 0.05$).

Regression analysis

In the MCI-HI group, the independent variables were the PTA and ABR scores of both the ears; the MMSE and the MoCA scores were the dependent variables for multiple linear regression analysis. The PTA score of the right ear at baseline was an important factor associated with the MoCA, visuospatial/executive, naming, and abstraction scores at 12-month follow-up ($\beta = -0.776$ to -0.422, $p < 0.05$). At the baseline, the ABR scores of both the ears were an important factor associated with the attention score ($\beta = -0.794$ to 0.781, $p < 0.01$) (Table 3).

Discussion

We measured the PTA, ABR, the MMSE, and the MoCA in community-based patients with MCI through a randomized, controlled, and longitudinal study to explore the correlation and long-term effect of HL and cognitive function in patients with MCI. To the best of our knowledge, this is the first study to focus on the effect of HL on cognitive function in patients with MCI by means of a randomized controlled study rather than by a cross-sectional survey, which is an original research direction. We found that HL was significantly negatively associated with cognitive function only in patients with MCI with HI, and was more significantly associated with cognitive function 1 year later. Meanwhile, the PTA of the right ear may be a predictor of cognitive decline after 1 year in patients with MCI with HI.

An English study of aging involving 14,767 adults aged 50 years and older showed that participants with self-reported

TABLE 2 Hearing and cognitive functions of participants in each group.

Variable	Follow-up	Overall ($n = 90$)	MCI-HI ($n = 30$)	MCI-nHI ($n = 30$)	nMCI ($n = 30$)	$F/\chi 2$	p
PTA, (mean ± SD)							
Left	B/L	26.22 ± 10.34	37.41 ± 10.17	18.86 ± 4.70	22.40 ± 1.48	68.36	<0.001**
	12M	33.81 ± 9.05	40.93 ± 7.72	27.84 ± 7.43	33.67 ± 5.84	30.03	<0.001**
	t (p)	−5.24 (<0.001**)	−1.51 (0.136)	−4.98 (<0.001**)	−10.24 (<0.001**)		
Right	B/L	25.74 ± 9.58	35.79 ± 9.93	20.62 ± 4.76	20.82 ± 1.93	54.46	<0.001**
	1 M	34.41 ± 8.76	37.83 ± 8.61	31.22 ± 8.06	32.18 ± 8.59	4.63	0.012*
	t (p)	−6.33 (<0.001**)	−0.85(0.398)	−6.20 (<0.001**)	−8.31 (<0.001**)		
ABR, (mean ± SD)							
Left	B/L	30.00 (10.00)	42.50 (15.00)	27.50 (5.00)	25.00 (8.00)	44.81	<0.001**
	12M	40.00 (20.00)	50.00 (15.00)	32.50 (11.00)	40.00 (11.00)	26.56	<0.001**
	z (p)	−5.47 (<0.001**)	−2.72 (0.006**)	−3.80 (<0.001**)	−5.10 (<0.001**)		
Right	B/L	30.00 (15.00)	40.00 (11.00)	27.50 (11.00)	25.00 (5.00)	46.74	<0.001**
	12M	40.00 (15.00)	50.00 (16.00)	35.00 (11.00)	40.00 (10.00)	29.67	<0.001**
	z (p)	−5.78 (<0.001**)	−2.55 (0.011*)	−3.59 (<0.001**)	−5.99 (<0.001**)		
MMSE, (mean ± SD)	B/L	25.00 (3.00)	24.00 (2.00)	24.00 (2.00)	28.50 (2.00)	58.43	<0.001**
	12M	25.00 (4.00)	23.50 (2.00)	24.00 (2.00)	27.50 (3.00)	53.12	<0.001**
	z (p)	−1.61 (0.108)	−1.89 (0.058)	−1.17 (0.243)	−0.94 (0.002**)		
MoCA, (mean ± SD)	B/L	23.00 (4.00)	22.00 (5.00)	23.00 (3.00)	26.00 (5.00)	22.71	<0.001**
	12M	22.00 (3.00)	21.00 (5.00)	22.00 (3.00)	24.00 (4.00)	23.716	<0.001**
	z (p)	−2.28 (0.022*)	−1.74 (0.082)	−1.03 (0.303)	−1.76 (0.001**)		
Visuospatial/executive	B/L	3.00 (1.00)	4.00 (2.00)	3.00 (0.00)	4.00 (2.00)	12.11	0.002**
	12M	3.00 (2.00)	2.00 (2.00)	3.00 (1.00)	3.00 (2.00)	6.769	0.034*
	z (p)	−2.60 (0.009**)	−1.20 (0.230)	−1.59 (0.112)	−2.27 (0.001**)		
Naming	B/L	3.00 (1.00)	3.00 (0.00)	2.50 (1.00)	3.00 (1.00)	13.72	0.001**
	12M	3.00 (0.00)	3.00 (1.00)	3.00 (0.00)	3.00 (0.00)	1.65	0.438
	z (p)	−1.12 (0.261)	−0.62 (0.538)	−1.98 (0.047*)	−1.22 (0.222)		
Attention	B/L	5.00 (1.00)	5.00 (1.00)	5.00 (0.00)	6.00 (1.00)	22.78	<0.001**
	12M	5.00 (2.00)	4.50 (1.00)	4.00 (1.00)	6.00 (0.00)	32.225	<0.001**
	z (p)	−0.95 (0.342)	−0.34 (0.736)	−2.99 (0.003**)	−0.89 (0.371)		
Language	B/L	2.00 (1.00)	2.00 (1.00)	2.00 (0.00)	3.00 (0.00)	17.38	<0.001**
	12M	2.00 (1.00)	2.00 (1.00)	2.00 (1.00)	3.00 (1.00)	5.18	0.075
	z (p)	−1.35 (0.178)	−1.03 (0.303)	−0.662 (0.508)	−1.93 (0.054)		
Abstraction	B/L	1.00 (1.00)	1.00 (2.00)	1.00 (1.00)	2.00 (1.00)	16.47	<0.001**
	12M	2.00 (0.00)	2.00 (1.00)	2.00 (0.00)	2.00 (0.00)	4.53	0.104
	z (p)	−5.07 (<0.001**)	−3.68 (<0.001**)	−5.06 (<0.001**)	−0.43 (0.671)		
Memory	B/L	3.00 (2.00)	2.50 (1.00)	2.50 (2.00)	3.00 (2.00)	0.36	0.837
	12M	2.00 (2.00)	1.00 (2.00)	2.00 (1.00)	3.00 (3.00)	15.44	<0.001**
	z (p)	−3.49 (<0.001**)	−3.95 (<0.001**)	−2.00 (0.045*)	−0.55 (0.583)		
Orientation	B/L	6.00 (0.00)	6.00 (1.00)	6.00 (0.00)	6.00 (0.00)	9.87	0.007**
	12M	6.00 (0.00)	6.00 (1.00)	6.00 (0.00)	6.00 (0.00)	7.62	0.022*
	z (p)	−0.25 (0.803)	−0.115 (0.909)	−1.00 (0.317)	−0.014 (0.989)		

MCI-HI, Mild cognitive impairment with hearing impairment; MCI-nHI, Mild cognitive impairment without hearing impairment; nMCI, No mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment (The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment), PTA, Pure tone audiometry, ABR, Auditory brainstem response; B/L, Baseline; 12M, 12-month; *$p < 0.05$, **$p < 0.01$.

or objective moderate and poor hearing were more likely to be diagnosed with dementia than those with normal hearing (Davies et al., 2017). A cross-sectional study of 995 Japanese adults aged 36–84 years suggested that HI was independently associated with a higher prevalence of MCI in elderly adults aged 60–69 and 70 years or older (Miyake et al., 2020). These findings

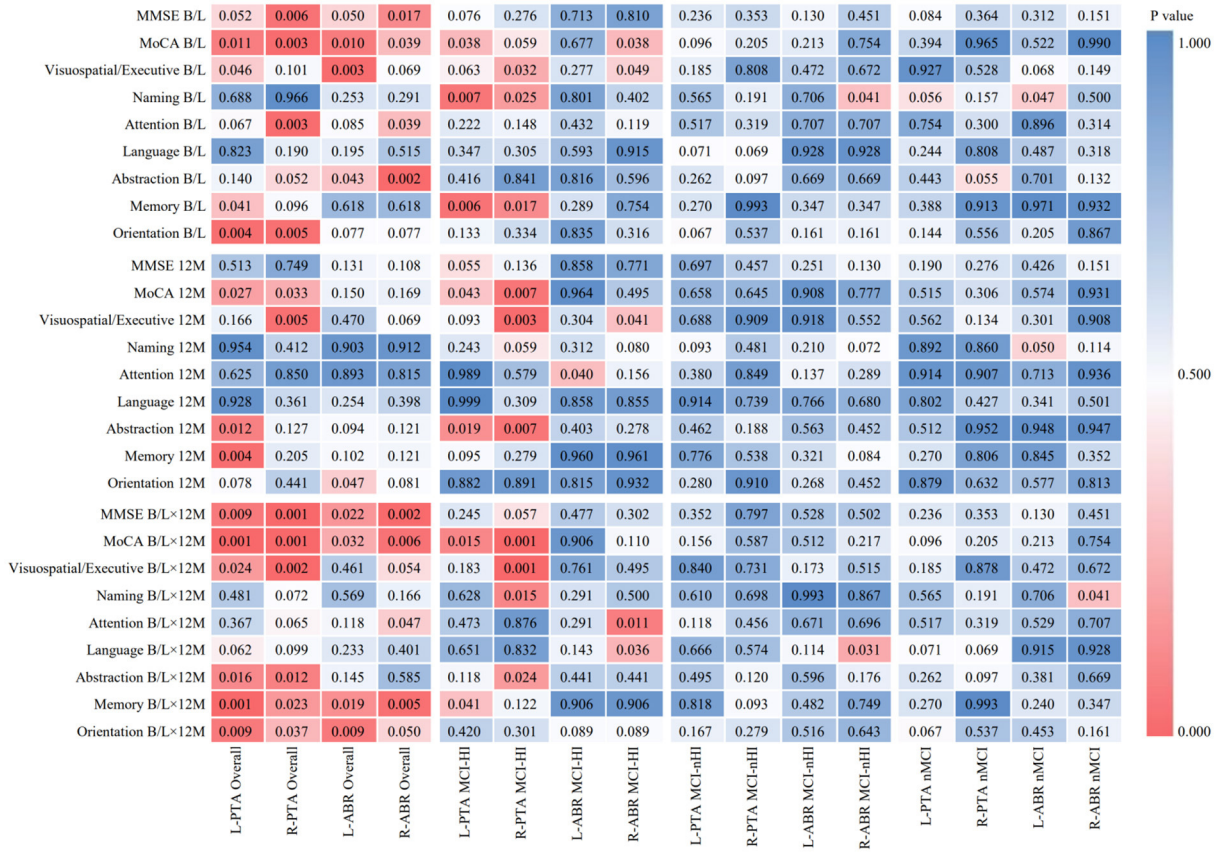

FIGURE 1
Heat map of correlation analysis between hearing and cognitive functions in different periods. MCI-HI, Mild cognitive impairment with hearing impairment; MCI-nHI, Mild cognitive impairment without hearing impairment; nMCI, No mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment (The Montreal Cognitive Assessment, MoCA, a brief screening tool for mild cognitive impairment), PTA, Pure tone audiometry, ABR, Auditory brainstem response; B/L, Baseline; 12M, 12-month; B/L×12 M, Baseline PTA and ABR scores × 12-month MMSE and MOCA scores.

are partially consistent with our results, but these studies did not explain the association of cognitive reserve with hearing loss and cognitive function. Chen and Lu (2020) found that hearing-impaired elderly with low cognitive reserve had the highest risk of cognitive impairment [odds ratio (OR) 4.32, 95% CI 3.42–5.47], further confirming that cognitive reserve moderated the negative association between hearing difficulties and cognitive function.

Some longitudinal studies of older adults have also confirmed the long-term effects of HI on cognitive function. In a 10-year cohort study conducted in the US, HI in patients and PTA > 25 dB were significantly positively associated with a 10-year risk of cognitive impairment in dementia or Alzheimer's disease (Fischer et al., 2016). In a meta-analysis of 15,521 subjects followed-up for 2–16.8 years, HI was associated with a higher risk of MCI [relative risk (RR) = 1.30, 95% CI: 1.12, 1.51] and dementia (RR = 2.39, 95% CI: 1.58, 3.61) (Wei et al., 2017). The Taiwan Longitudinal Study on Aging (TLSA) with a mean follow-up of 8.9 ± 3.9 years showed that HL was an independent risk factor for cognitive impairment other than geriatric syndromes (Tai et al., 2021). However, these studies did not group patients by the presence or absence of HI and were unable to show the association of HI with cognitive function in MCI subgroups.

There are also many different views on the impact of binaural hearing differences on cognitive function. A controlled study of patients with tinnitus and normal adults showed that the tinnitus group performed significantly worse in the left ear than in the right ear, and this interaural difference may be influenced by a right-ear advantage for speech sounds, possibly interacting with cognitive factors (Tai and Husain, 2018). In the PTA and brain MRI study of 982 older adults, mild right ear HL in older women was associated with left frontal and bilateral occipital cortical thinning and mild-to-severe right ear HL was associated with bilateral frontal, right temporal, and bilateral occipital cortical thinning (Ha et al., 2020). A

TABLE 3 Multiple linear regression analysis of hearing and cognitive functions in the MCI-HI group.

Variable	Follow-up	PTA								ABR							
		Left				Right				Left				Right			
		β	*t*	*p*	VIF	β	*t*	*p*	VIF	β	*t*	*p*	VIF	β	*t*	*p*	VIF
MMSE	B/L	−0.347	−1.480	0.151	1.618	−0.120	−0.557	0.582	1.374	0.203	0.699	0.491	2.494	0.006	0.019	0.985	2.596
	12M	−0.569	−2.018	0.054	2.656	−0.114	−0.506	0.617	1.679	0.475	1.481	0.151	3.441	−0.080	−0.260	0.797	3.130
	B/L × 12M	−0.032	−0.139	0.891	1.618	−0.239	−1.126	0.271	1.374	0.328	1.149	0.261	2.494	−0.402	−1.378	0.180	2.596
MoCA	B/L	−0.178	−0.831	0.414	1.374	−0.178	−0.831	0.414	1.374	0.347	1.204	0.240	2.494	−0.286	−0.970	0.341	2.596
	12M	−0.389	−1.500	0.146	2.656	−0.400	−1.941	0.064	1.679	0.440	1.493	0.148	3.441	−0.078	−0.278	0.783	3.130
	B/L × 12M	−0.004	−0.019	0.985	1.618	−0.448	−2.290	0.031*	1.374	0.176	0.669	0.510	2.494	−0.296	−1.100	0.282	2.596
Visuospatial/executive	B/L	0.036	0.160	0.874	1.618	−0.347	−1.660	0.109	1.374	−0.052	−0.184	0.856	2.494	−0.210	−0.730	0.472	2.596
	12M	0.052	0.190	0.851	2.656	−0.413	−1.880	0.072	1.679	0.243	0.775	0.446	3.441	−0.389	−1.299	0.206	3.130
	B/L × 12M	0.297	1.637	0.114	1.618	−0.776	−4.643	0.000**	1.374	−0.003	−0.013	0.990	2.494	−0.063	−0.276	0.785	2.596
Naming	B/L	0.288	1.253	0.222	1.618	0.208	0.981	0.336	1.374	−0.065	−0.229	0.821	2.494	0.044	0.151	0.881	2.596
	12M	−0.114	−0.382	0.706	2.656	−0.118	−0.498	0.623	1.679	0.204	0.599	0.554	3.441	−0.386	−1.190	0.245	3.130
	B/L × 12M	0.019	0.096	0.925	1.618	−0.597	−3.258	0.003**	1.374	0.066	0.266	0.792	2.494	0.316	1.255	0.221	2.596
Attention	B/L	−0.056	−0.270	0.789	1.618	−0.009	−0.046	0.964	1.374	0.781	3.014	0.006**	2.494	−0.794	−3.002	0.006**	2.596
	12M	−0.423	−1.526	0.140	2.656	−0.128	−0.583	0.565	1.679	0.650	2.061	0.050	3.441	0.044	0.145	0.886	3.130
	B/L × 12M	0.006	0.029	0.977	1.618	0.155	0.754	0.458	1.374	0.321	1.159	0.257	2.494	−0.705	−2.498	0.019*	2.596
Language	B/L	0.044	0.182	0.857	1.618	0.277	1.254	0.221	1.374	0.367	1.234	0.229	2.494	−0.359	−1.184	0.247	2.596
	12M	−0.010	−0.032	0.975	2.656	−0.310	−1.268	0.216	1.679	0.151	0.430	0.671	3.441	−0.094	−0.280	0.782	3.130
	B/L × 12M	0.213	0.948	0.352	1.618	−0.055	−0.266	0.792	1.374	−0.199	−0.714	0.482	2.494	−0.368	−1.293	0.208	2.596
Abstraction	B/L	−0.180	−0.738	0.467	1.618	−0.039	−0.172	0.865	1.374	−0.273	−0.900	0.377	2.494	0.414	1.337	0.193	2.596
	12M	−0.348	−1.315	0.200	2.656	−0.420	−1.995	0.057	1.679	0.091	0.301	0.766	3.441	0.129	0.448	0.658	3.130
	B/L × 12M	−0.162	−0.726	0.474	1.618	−0.422	−2.058	0.048*	1.374	−0.117	−0.424	0.675	2.494	0.357	1.266	0.217	2.596
Memory	B/L	−0.522	−2.647	0.014*	1.618	−0.250	−1.376	0.181	1.374	0.315	1.288	0.210	2.494	0.114	0.458	0.651	2.596
	12M	−0.555	−1.916	0.067	2.656	−0.124	−0.539	0.595	1.679	0.239	0.724	0.476	3.441	0.240	0.763	0.453	3.130
	B/L × 12M	−0.378	−1.626	0.116	1.618	−0.103	−0.482	0.634	1.374	0.139	0.481	0.634	2.494	−0.003	−0.009	0.993	2.596
Orientation	B/L	0.073	0.305	0.763	1.618	−0.355	−1.611	0.120	1.374	−0.041	−0.139	0.891	2.494	−0.045	−0.149	0.883	2.596
	12M	−0.072	−0.224	0.825	2.656	0.052	0.205	0.840	1.679	0.230	0.628	0.536	3.441	−0.265	−0.760	0.454	3.130
	B/L × 12M	−0.019	−0.076	0.940	1.618	−0.022	−0.094	0.926	1.374	−0.013	−0.043	0.966	2.494	−0.171	−0.542	0.593	2.596

MCI-HI, Mild cognitive impairment with hearing impairment; PTA, Pure tone audiometry, ABR, Auditory brainstem response; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; B/L, Baseline; 12M, 12-month; B/L × 12M, Baseline PTA and ABR scores × 12-month MMSE and MOCA scores; *$p < 0.05$, **$p < 0.01$.

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controlled study of 400 right-handed participants showed a right ear advantage in auditory processing, possibly corresponding to a left hemispheric advantage in verbal and nonverbal imagery (Prete et al., 2016). This also confirms our findings that hearing in the right ear is associated with areas of brain auditory feedback and cognitive function dominance, and that HL in the right ear compared to the left ear may be a predictor for the early identification of MCI. Additionally, it may help primary healthcare clinicians to prevent MCI by screening and intervening in elderly patients with HL.

Limitations

We also note several limitations. First, research has been greatly limited with respect to expanding the number of samples because of the COVID-19 pandemic, and the current sample group is limited to individuals aged 55–65 years. Second, we did not extend brain imaging tests such as functional MRI (fMRI) or diffusion tensor imaging (DTI) to elucidate the relationship between HL, cognitive decline, and structural or functional features of the brain (Wang et al., 2021). Future studies should further explore whether the intervention of HL can reduce the risk of MCI in elderly patients, expand the study with 2-, 5- and 10-year follow-up periods, and observe the final outcome of the impact of HL on cognitive function. These studies would provide the exact mechanism to achieve an optimal effect in the early identification of MCI.

Conclusion

In this study, HL was significantly negatively associated with cognitive function only in patients with MCI with HI, and the PTA of the right ear may be a predictor of cognitive decline after 1 year in patients with MCI with HI. This information may help primary healthcare clinicians to prevent MCI by screening and intervening in care for elderly patients with HL.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the Shanghai Pudong New Area Mental Health Center and Tongji University School of Medicine (No: PDJWLL2019017). The patients/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

JT, JZ, and JY: data analysis and writing—original draft preparation and revising. XS and JY: conceptualization and writing—reviewing and editing. LX: hearing function testing, analysis, and interpretation. JT and JZ: supervision. JM: project administration. ML, MY, XC, and QZ: sample collection. All authors have approved the submitted version of the manuscript.

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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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Non-linear association between serum spermidine and mild cognitive impairment: Results from a cross-sectional and longitudinal study

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Background: Although animal studies show that spermidine (SPD) affects cognitive function, the relevant evidence among humans is limited. We aim to examine the association between serum SPD levels and cognitive performance.

Materials and Methods: We conducted a cross-sectional and longitudinal study including a baseline and one follow-up survey. The baseline survey was conducted from June 2019 to August 2019, while the follow-up survey was conducted from June 2021 to August 2021. We analyzed 3,774 adult participants aged >35 years, who had no history of dementia.

Results: The mean (SD) age of the participants was 57.4 (9.8) years. Relative to the first tertile, the multivariate-adjusted ORs (95% CIs) of mild cognitive impairment (MCI) for the second and third tertile groups were 0.78 (0.65, 0.93) and 0.80 (0.67, 0.96), respectively. Restricted cubic spline models show that there is a non-linear association between SPD and MCI. In line with cross-sectional findings, the longitudinal study showed that a high SPD concentration may indicate a lower risk of MCI [ORs (95% CIs) for the third tertile of 0.62 (0.39, 0.99)].

Conclusion: Our findings suggest that SPD is favorable for cognitive function. Monitoring the SPD levels may help reduce the incidence of MCI, hence decreasing the burden of MCI.

KEYWORDS

spermidine, cognition, mild cognitive impairment, longitudinal study, rural

Introduction

Dementia is the leading cause of disability among people aged over 65 years worldwide. From 1990 to 2016, the global number of dementia patients more than doubled, from 20.2 to 43.8 million (GBD 2016 Dementia Collaborators, 2019). People with dementia in China account for approximately 25% of the dementia patients (Jia et al., 2020) worldwide. This scenario has imposed a heavy socioeconomic burden, impacting their quality of life. Although China has established and implemented a series of programs to manage this disease in the past decade, patients in rural areas often have difficulty accessing health services compared with patients in urban areas (Xue et al., 2018). Meanwhile, no specific therapy is available for the treatment of dementia. Therefore, early identification of high-risk populations and improvement of prognostic factors are critical, especially for people living in rural areas.

Mild cognitive impairment (MCI), the stage between normal cognition (NC) and dementia, is associated with a higher risk of dementia. Previous studies have shown that approximately 16% of patients diagnosed with MCI return to normal or near-normal cognition after a year of treatment (Koepsell and Monsell, 2012). Thus, identifying more sensitive or specific biomarkers for MCI is essential to reduce the burden of dementia.

Spermidine (SPD) is a natural polyamine present in all living organisms, and play a key role in maintaining cellular homeostasis. This chemical contributes to various critical cellular functions, including cell growth and proliferation, tissue regeneration, DNA and RNA stabilization, enzymatic modulation, and regulation of translation (Madeo et al., 2019). The association between SPD and cognition has been explored using animal experiments. Gupta et al. (2013) demonstrated that fruit flies fed SPD showed enhanced autophagy and that SPD can effectively inhibit aging-associated memory impairment via autophagy. A recent study revealed that dietary SPD passes the blood–brain barrier and improves spatial and temporal memory in aged mice (Schroeder et al., 2021).

Several small randomized controlled clinical trials have been implemented to examine the relationship between dietary SPD supplements and cognition in humans; however, the conclusions have been inconsistent (Wirth et al., 2018; Pekar et al., 2021). Additionally, a prospective cohort study involving 815 participants found that higher nutritional SPD intake is associated with a lower risk for cognitive impairment and decline (Schroeder et al., 2021). However, self-reported dietary information obtained from food frequency questionnaires is subject to measurement error that could be attributed to recall bias and social desirability. Dietary SPD intake may not entirely reflect the actual SPD concentration in the body. The present study examines SPD levels in serum to objectively reflect the concentration of SPD in the body and provide a more objective basis for subsequent promotion and application.

Therefore, we explore the association between serum SPD levels and MCI based on the mutual verification of cross-sectional and longitudinal studies conducted on a Chinese population.

Abbreviations: SPD, spermidine; SD, standard deviation; MCI, mild cognitive impairment; ORs, odds ratios; CI, confidence interval; MoCA, Montreal cognitive assessment; MoCA-BC, Montreal cognitive assessment-basic for Chinese; SCD, subjective cognitive decline; FAQ, functional activities questionnaire; HPLC, high-performance liquid chromatography; FLD, fluorescence detector; ACN, acetonitrile; NIA-AA, National Institute on Aging-Alzheimer's association; DSM-V, the fifth edition of the diagnostic and statistical manual of mental disorders; NC, normal cognition; BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; ROC, receiver operating characteristic curves; AUC, areas under the curves; NRI, net reclassification index; IDI, integrated discrimination improvement.

Materials and methods

Study population

We derived the data from a large-scale longitudinal study. The baseline survey was conducted from June 2019 to August 2019 in the rural areas of Fuxin County, Liaoning Province, China. Based on the demographic characteristics, two townships were selected from the southern region and one township was chosen from the northern and eastern regions of the county. A total of 33 villages were selected from these four townships. The inclusion criteria for participants included: (1) ≥35 years old; (2) a local residence time ≥5 years; and (3) signed informed consent. The exclusion criteria included: (1) pregnancy; (2) severe liver and renal failure; and (3) unwillingness to participate in this study. A total of 4,689 participants were recruited for the study. The follow-up survey was conducted from June 2021 to August 2021 with the same inclusion and exclusion criteria at baseline. In conclusion, 2,046 participants were enrolled as the longitudinal study population. Written informed consent was obtained from all participants. In the case of illiterate participants, we obtained written informed consents from their proxies. The procedures followed were performed under the ethical standards of the responsible committee on human experimentation of China Medical University ([2018]083).

Figure 1 shows a flowchart of the participants included in the current analysis. Of the 4,689 participants, those with missing information about Montreal cognitive assessment (MoCA) score ($n = 437$), SPD ($n = 92$), and confounding factors ($n = 44$) at baseline were excluded. Additionally, 342 participants with a history of stroke, brain atrophy, traumatic brain injury, depression, or dementia at baseline were excluded. At baseline, dementia was defined as a self-reported dementia diagnosis by a physician. In conclusion, 3,774 participants were enrolled in the cross-sectional analysis. For the longitudinal study, 2,046

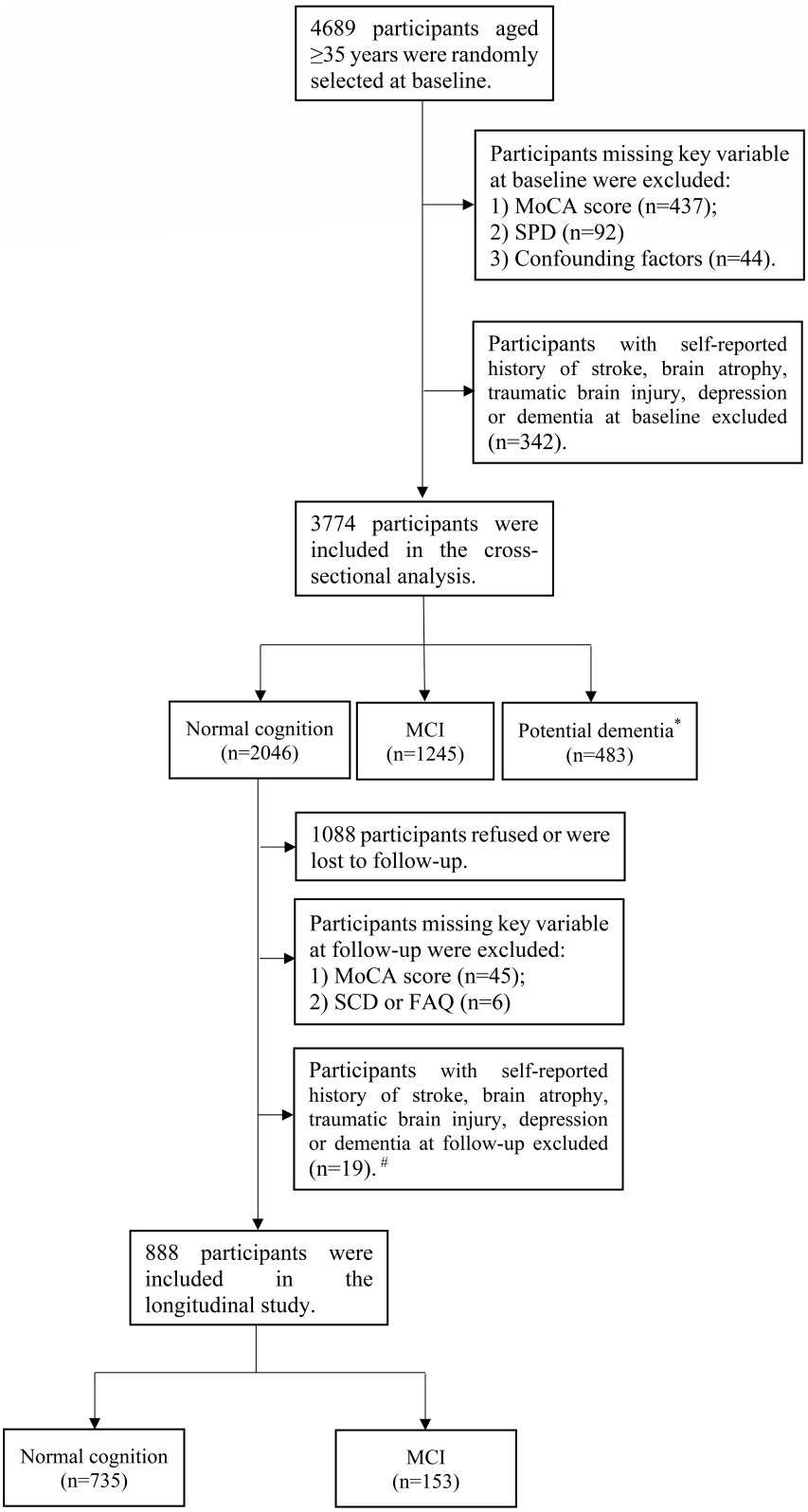

FIGURE 1
Flowchart of the participants included in the current analysis. *Potential dementia was defined following MoCA-BC. #Dementia was diagnosed following the criteria of the NIA-AA workgroup.

participants with NC were declared eligible to attend the follow-up. Among these participants, 1,088 participants refused or were lost to follow-up. We further excluded participants with missing Montreal cognitive assessment-basic for Chinese (MoCA-BC) scores (n = 45) and subjective cognitive decline (SCD), or functional activities questionnaire (FAQ) (n = 6) at follow-up. Participants with a history of stroke, brain atrophy, traumatic brain injury, depression or dementia were also excluded at follow-up (n = 19). A total of 888 participants were enrolled in the longitudinal study.

Measurement of serum spermidine

The participants were examined after an overnight fast. Blood samples were drawn from the antecubital vein in the morning and were collected into siliconized vacuum glass tubes. Serum was obtained by centrifugation at 3,000 rpm for 10 min and then stored at −80°C until further analysis. SPD levels in serum were measured using high-performance liquid chromatography with a fluorescence detector (HPLC-FLD). The main process of detecting serum SPD was as follows: SPD trihydrochloride was performed by adding 200 μL 0.1 M HCl to 100 μL serum. Protein precipitation was further conducted by adding 1 mL acetonitrile (ACN) to the mixture to precipitate the serum proteins. The supernatant was blown to dryness, following which 200 μL of 0.1 M HCl was added to reconstitute the dried product. Derivatization was performed by adding 200 μL dansyl chloride and 400 μL buffer to the above 200 μL reconstituted product. This was followed by vortexing, incubation in a water bath at 60°C for 45 min, cooling to room temperature, adding 40 μL ammonia water, incubation in the dark for 30 min, and making up the volume to 1 mL using ACN. This final solution was mixed well and passed through a 0.22 μm filter. The extracted samples were analyzed using an HPLC system to obtain a standard curve. The mobile phase solutions labeled A and B were ultrapure water and ACN, respectively. Gradient elution was performed as stated: 0–7 min: 55–50% A, 7–25 min: 50–10% A, 25–31 min: 10% A, 31–35 min: 10–55% A, and 35–40 min: 55% A. The flow rate was maintained at 0.8 mL/min and the column temperature was set to 35°C, while the detection wavelength was $\lambda_{ex}/\lambda_{em}$ = 340/510 nm.

Mild cognitive impairment assessment

The Chinese version of the MoCA-BC is routinely used to screen the MCI of older Chinese adults with different education levels and this is a 30-point test covering nine cognitive domains. **Supplementary Table 1** shows details on the components and corresponding maximum scores for each domain. At baseline, we only used MOCA-BC to screen for MCI and potential dementia. The optimal MoCA-BC cutoff scores used for MCI assessment were 19 for individuals with six or fewer years of education, 22 for those with 7–12 years of education, and 24 for those with more than 12 years of education (Chen et al., 2016). Participants with MoCA-BC scores <13 for individuals with six or fewer years of education, <15 for those with 7–12 years of education, and <16 for those with more than 12 years of education were potentially considered to have dementia (Huang et al., 2018).

At follow-up, the diagnosis of MCI was based on the criteria proposed by the National Institute on Aging-Alzheimer's association (NIA-AA) workgroup (Albert et al., 2011). The criteria included the following: (1) cognitive complaints from participants confirmed by an informant (relatives/doctors), which were assessed using the SCD scale; (2) objective evidence of impairment in one or more cognitive domains, which were assessed using the MoCA-BC in this study; and (3) independence of daily functional ability, which was measured using FAQ. A score of FAQ ≥5 was defined as dysfunction consistent with dementia divided from NC; and (4) no dementia, based on the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-V) (Sachdev et al., 2014).

Assessment and definition of other variables

Relevant data on demographic variables (age, sex, ethnicity, and education level), lifestyle factors (smoking and alcohol consumption), and history of disease were collected using a standardized questionnaire. Smokers were defined as people who smoked at least one cigarette per day and continued to smoke for a minimum of 6 months, while drinkers were defined as people who take at least three drinks every week for a minimum of 6 months.

Height and weight were measured using standardized procedures. Body mass index (BMI) was calculated in terms of weight (kg)/height $(m)^2$. According to the American Heart Association protocol, blood pressure (BP) was measured three times for at least 1 min after a minimum rest of 5 min between each measurement using a standardized automatic electronic BP measuring instrument (HEM-8102A/K) (O'Brien et al., 1990). The participants were instructed to avoid alcohol consumption, cigarette smoking, coffee/tea, and exercise for at least 30 min before the BP measurement. The average of three BP values was used for the final analysis and evaluation. Hypertension was taken as an antihypertensive medication in the last 2 weeks, diastolic blood pressure (DBP) ≥90 mmHg or systolic blood pressure (SBP) ≥140 mmHg (Joint Committee for Guideline Revision, 2019). Fasting blood samples were collected in the morning from participants who had fasted for at least 8 h. Fasting serum glucose was measured using a hexokinase method using the Roche Cobas 8000 C701 automatic

TABLE 1 Baseline characteristics stratified by spermidine (SPD) tertile.[a]

Characteristic	Total	T1 (<16.69 ng/ml)	T2 (16.69–37.29 ng/ml)	T3 (≥37.29 ng/ml)	*P*
Female, No. (%)	2,178 (66.2)	769 (70.3)	766 (69.3)	643 (58.9)	<0.001
Age, y	57.4 ± 9.8	57.2 ± 9.3	57.2 ± 9.9	58.0 ± 10.1	0.057
Ethnicity, No. (%)					0.367
Han ethnicity	2,134 (64.8)	685 (62.6)	726 (65.7)	723 (66.2)	
Mongolian	1,012 (30.8)	362 (33.1)	330 (29.9)	320 (29.3)	
Others	145 (4.4)	47 (4.3)	49 (4.4)	49 (4.5)	
Education level, No. (%)					0.805
Illiterate or primary school	1,279 (38.9)	417 (38.1)	431 (39.0)	431 (39.5)	
Junior high school	1,507 (45.8)	498 (45.5)	513 (46.4)	496 (45.4)	
Tertiary high school or higher	505 (15.3)	179 (16.4)	161 (14.6)	165 (15.1)	
Drinker, No. (%)	951 (28.9)	297 (27.1)	295 (26.7)	359 (32.9)	0.002
Smoker, No. (%)	1,129 (34.3)	358 (32.7)	351 (31.8)	420 (38.5)	0.002
History of CHD, No. (%)	432 (13.1)	145 (13.3)	131 (11.9)	156 (14.3)	0.238
Antihypertensive medicine use, No. (%)	226 (6.9)	175 (16.0)	180 (16.3)	157 (14.4)	0.413
Hypoglycemic medicine or insulin, No. (%)	512 (15.6)	82 (7.5)	78 (7.1)	66 (6.0)	0.388
BMI, kg/m^2	24.8 ± 3.7	24.7 ± 3.8	24.5 ± 3.6	25.2 ± 3.8	<0.001
SBP, mmHg	132.6 ± 20.8	132.1 ± 20.8	131.5 ± 20.3	134.3 ± 21.2	0.003
DBP, mmHg	80.5 ± 11.1	80.0 ± 10.7	80.2 ± 10.9	81.3 ± 11.7	0.008
Fasting glucose, mmol/L	5.9 ± 1.7	5.9 ± 2.0	5.8 ± 1.5	5.8 ± 1.6	0.096
SPD, median (IQR), ng/mL	24.84 (13.41–49.28)	10.81 (9.13–13.39)	24.84 (20.89–30.77)	65.01 (49.28–95.99)	<0.001

SPD, spermidine; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; SD, standard deviation; IQR, interquartile range.
[a]Unless otherwise indicated, data are expressed as the mean ± SD.

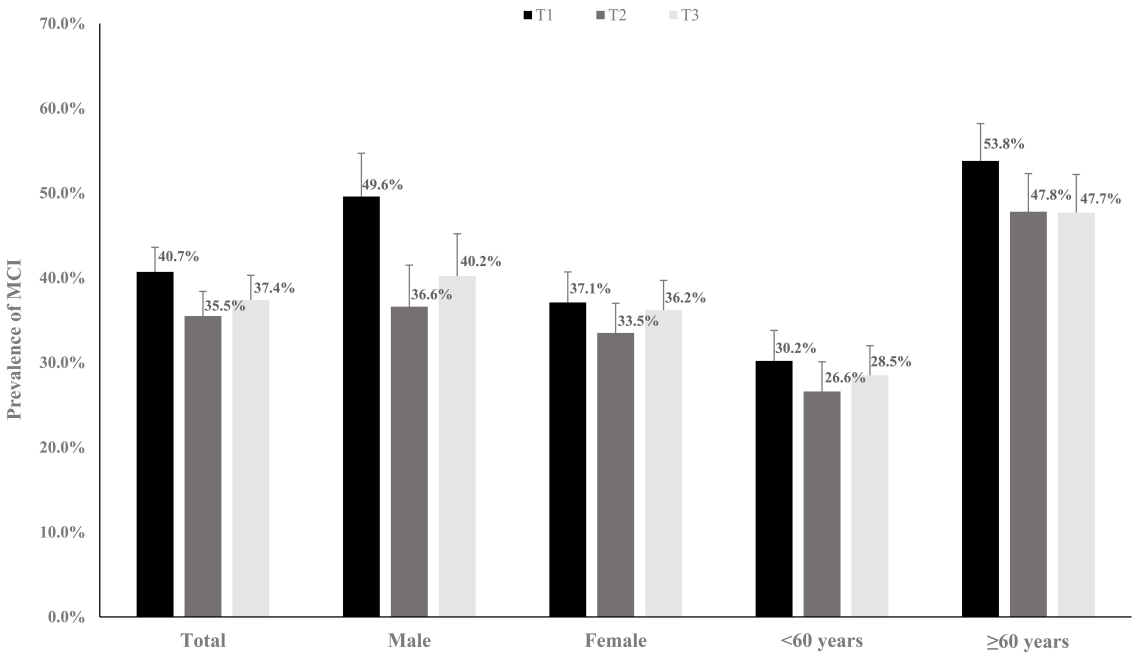

FIGURE 2
The prevalence rates (95% CI) of mild cognitive impairment (MCI) grouping by different spermidine (SPD) levels.

TABLE 2 Association between serum SPD levels and prevalent MCI.[a]

	T1	T2	T3	*P*-value for non-linear trend
Total (*N* = 3,291), OR (95% CI)				
Events	445	392	408	
Model 1	1.00 (Ref.)	0.78 (0.66, 0.94)	0.80 (0.67, 0.95)	<0.001
Model 2	1.00 (Ref.)	0.78 (0.65, 0.93)	0.80 (0.67, 0.96)	<0.001
Male (*N* = 1,113), OR (95% CI)				
Events	187	133	150	
Model 1	1.00 (Ref.)	0.56 (0.42, 0.76)	0.63 (0.47, 0.85)	<0.001
Model 2	1.00 (Ref.)	0.56 (0.41, 0.76)	0.64 (0.47, 0.87)	< 0.001
Female (*N* = 2,178), OR (95% CI)				
Events	269	243	263	
Model 1	1.00 (Ref.)	0.86 (0.69, 1.07)	0.94 (0.75, 1.17)	0.107
Model 2	1.00 (Ref.)	0.85 (0.68, 1.06)	0.93 (0.75, 1.17)	0.108
<60 years (*N* = 1,845), OR (95% CI)				
Events	186	163	176	
Model 1	1.00 (Ref.)	0.86 (0.66, 1.10)	0.93 (0.72, 1.20)	0.045
Model 2	1.00 (Ref.)	0.86 (0.67, 1.12)	0.93 (0.72, 1.20)	0.045
≥60 years (*N* = 1,446), OR (95% CI)				
Events	260	230	230	
Model 1	1.00 (Ref.)	0.77 (0.60, 1.00)	0.74 (0.58, 0.96)	0.004
Model 2	1.00 (Ref.)	0.76 (0.58, 0.98)	0.76 (0.59, 0.98)	0.004

N, number of participants; SPD, spermidine; OR, odds ratio; CI, confidence interval; MCI, mild cognition impairment.
[a]ORs and CIs were calculated using logistic regression models. Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, ethnicity, education levels, smoking, drinking, body mass index, history of hypertension, diabetes, and coronary heart disease.

biochemical analyzer in an accredited central laboratory. All the laboratory equipment was calibrated, and the blood samples of all the populations were randomly coded and tested blindly to effectively eliminate any systematic error, bias, or variability of laboratory batch measurements. Diabetes mellitus was defined as a condition in which fasting serum glucose was ≥7.0 mmol/L, using hypoglycemic drugs or insulin, or self-report of diabetes diagnosis by a physician or other health professional (Wang et al., 2021).

Statistical analysis

Normally distributed data are expressed as the mean ± SD; SPD levels with a skewed distribution are reported as medians (interquartiles) and ln transformed to ensure approximate normality before analysis. Categorical variables are represented using frequency and percentage. Characteristics were compared using the one-way analysis of variance, non-parametric analysis or χ^2 test, as appropriate. Multivariate logistic regression models were used to calculate the odds ratios (ORs) with 95% confidence interval (CI) for the relationships between SPD and MCI or cognitive domain dysfunction, adjusting for age, sex, ethnicity, education levels, smoking, drinking, BMI, history of hypertension, diabetes, and coronary heart disease (CHD). SPD entered the model as a tertile (T1: <16.69 ng/mL, T2: 16.69–37.29 ng/mL, T3: ≥37.29 ng/mL), with the lowest tertile (T1) as the reference group. We also used restricted cubic splines with three knots at the 25th, 50th, and 75th centiles to flexibly model the relationship of SPD with MCI. Additionally, receiver operating characteristic (ROC) curves were constructed, and the areas under the curves (AUCs) were calculated to assess the discriminant power of SPD for MCI. We further examined whether adding Ln (SPD) could improve the net reclassification index (NRI) and/or integrated discrimination improvement (IDI) for MCI. All analyses were conducted using SPSS 22.0 (IBM SPSS Inc., Chicago, IL, United States) and SAS statistical software (version 9.4, SAS Institute Inc., Cary, NC, United States).

Results

Table 1 shows the baseline characteristics of the 3,291 participants stratified by the SPD tertile. In total, the mean (SD) age was 57.4 (9.8) years. Sex, alcohol consumption, smoking, SBP, DBP, and BMI at baseline significantly differed among the three groups. Figure 2 shows the prevalence (95% CI) of MCI at baseline. The prevalence (95% CIs) of MCI for participants in the first, second, and third tertile groups was 40.7% (37.8, 43.6%), 35.5% (32.6, 38.8%), and 37.4% (34.5, 40.2%), respectively.

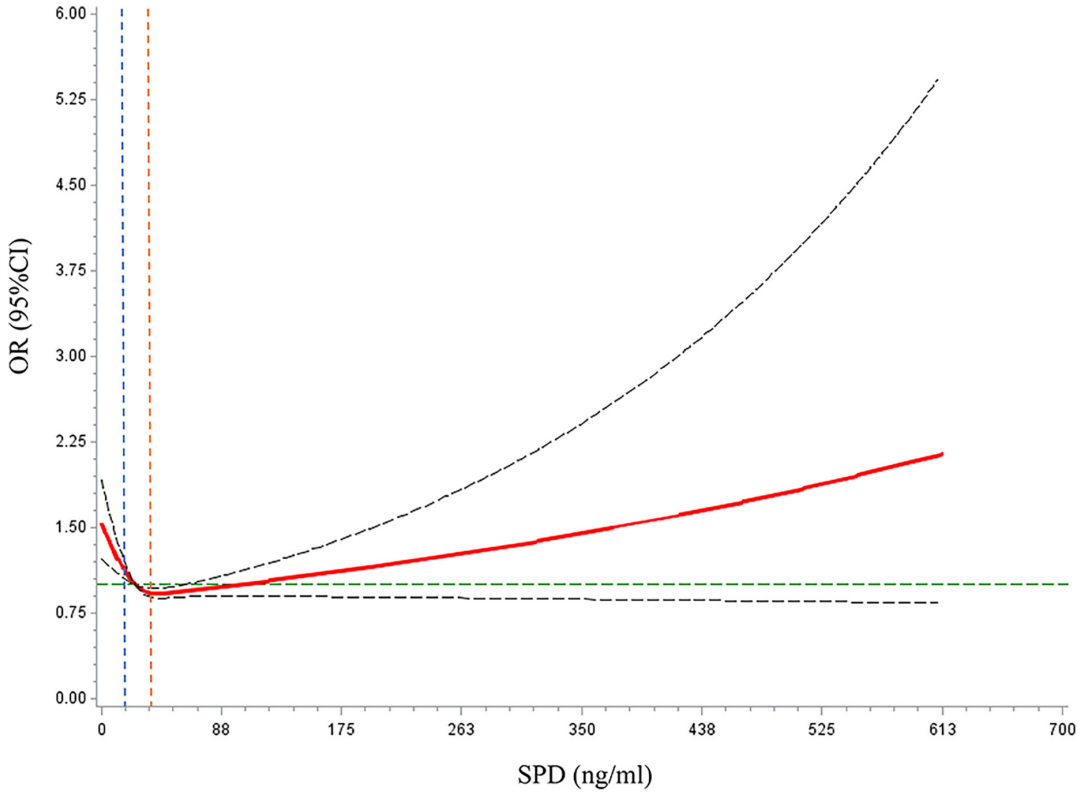

FIGURE 3
Dose–response relationships between spermidine (SPD) and mild cognitive impairment (MCI) prevalence. The solid red line represents the dose–response curve. The dashed black lines represented the 95% confidence interval. The dashed green line represents the reference line for OR = 1. The blue dashed line represents the reference line for the first tertile of SPD (SPD = 16.69 ng/ml). The orange dashed line represents the reference line for the third tertile of SPD (SPD = 37.29 ng/ml).

In cross-sectional analyses, high concentrations of serum SPD were associated with low MCI prevalence (Table 2). After adjusting for age, sex, ethnicity, education levels, smoking, drinking, BMI, history of hypertension, diabetes, and CHD, compared with the first tertile, the multivariate-adjusted ORs (95% CIs) for the second and third tertiles were 0.78 (0.65, 0.93) and 0.80 (0.67, 0.96), respectively.

In the subgroup analysis, we only observed an relationship between SPD and MCI among males and the subgrouping of participants into under 60 and over 60 years. After adjusting for age, ethnicity, education levels, smoking, drinking, BMI, history of hypertension, diabetes, and CHD in males, compared with the first tertile, the multivariate-adjusted ORs (95% CIs) for the second and third tertiles were 0.56 (0.41, 0.76) and 0.64 (0.47, 0.87), respectively. In people aged <60, after adjusting for confounding factors, compared with the first tertile, the multivariate-adjusted ORs (95% CIs) for the second and third tertiles were 0.86 (0.67, 1.12) and 0.93 (0.72, 1.20), respectively. In people aged >60, after adjusting for confounding factors, compared with the first tertile, the multivariate-adjusted ORs (95% CIs) for the second and third tertiles were 0.76 (0.58, 0.98) and 0.76 (0.59, 0.98), respectively.

TABLE 3 Association between serum SPD levels and incident MCI.[a]

	T1	T2	T3	*P*-value for non-linear trend
Total (*N* = 888), OR (95% CI)				
Events	62	49	42	
Model 1	1.00 (Ref.)	0.78 (0.51, 1.20)	0.61 (0.39, 0.95)	0.256
Model 2	1.00 (Ref.)	0.76 (0.49, 1.18)	0.62 (0.39, 0.99)	0.318

N, number of participants; SPD, spermidine; OR, odds ratio; CI, confidence interval; MCI, mild cognition impairment.
[a]ORs and CIs were calculated using logistic regression models. Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, ethnicity, education levels, smoking, drinking, body mass index, history of hypertension, diabetes, coronary heart disease, and baseline MoCA-BC score.

Restricted cubic spline models were used to evaluate the relationship between SPD and MCI (Figure 3). In multi-adjusted models, the relationships between SPD and MCI were non-linear (*P* for non-linear <0.001).

The ROC curves for the risk of MCI prevalence from multivariable logistic regression models, with and without SPD, were analyzed. The end points were characterized by

MCI; therefore, the first model to incorporate age, sex, ethnicity, education level, smoking, drinking, BMI, history of hypertension, diabetes, and CHD had an AUC of 0.666 (95% CI: 0.648–0.685). Ln (SPD) was supplemented to Model 2 with an AUC of 0.668 (95% CI: 0.649–0.687). The difference in AUC was statistically insignificant, suggesting that the discriminative abilities of the two models were similar. Adding Ln (SPD) improved risk reclassification for MCI events, measured by continuous NRI (0.079; 95% CI, 0.009–0.149; $P = 0.016$) and by IDI (0.002; 95% CI, 0.000–0.003; $P = 0.028$). The NRI and IDI results showed that the power of the reclassification of the new model was significantly improved.

Additionally, we explored the relationship between SPD and different cognitive domains (**Supplementary Table 2**). In total, compared with the first tertile, the third tertile group had a decreased risk of fluency, orientation, calculation, abstract, and visual perception dysfunction, with multivariate-adjusted ORs (95% CIs) of 0.78 (0.63, 0.97), 0.78 (0.65, 0.94), 0.80 (0.67, 0.96), 0.79 (0.65, 0.96), and 0.76 (0.59, 0.96), respectively.

To further validate the above results, we analyzed the relationship between serum SPD levels and MCI prevalence using a longitudinal study (**Table 3**). After adjusting for age, sex, ethnicity, education levels, smoking, drinking, BMI, history of hypertension, CHD, and diabetes, and baseline MoCA-BC score, compared with the first tertile, ORs (95% CIs) for the second and third tertiles were 0.76 (0.49, 1.18) and 0.62 (0.39, 0.99), respectively.

Discussion

We explored the role of serum SPD levels in MCI among 3,774 participants based on a large-scale epidemiological survey. We found a non-linear correlation between serum SPD levels and prevalent MCI events, which also showed potential of SPD to be a clinically useful indicator of MCI by improving risk reclassification. Similarly, in the longitudinal study, higher baseline SPD levels may indicate a lower risk of MCI events. To the best of our knowledge, this is the first study revealing the association of serum SPD levels with MCI in a large-scale population.

The relationship between SPD and cognition has been proven in animal experiments (Gupta et al., 2013; Hofer et al., 2021; Schroeder et al., 2021). Hofer et al. (2021) found that SPD is involved in preserving mitochondria and cognitive function. In aged fruit flies, simple SPD feeding suppressed age-induced memory impairment (Gupta et al., 2013). Most previous population studies on SPD and cognition examine dietary SPD (Wirth et al., 2018; Schwarz et al., 2020; Schroeder et al., 2021). A study involving 56 participants having cognitive declines and 47 healthy control participants showed that higher SPD intake might be a promising dietary approach to preserve brain health among older adults (Schwarz et al., 2020). The Bruneck Study shows that higher nutritional SPD intake is related to enhanced cognition in humans (Schroeder et al., 2021). A randomized controlled trial involving 30 participants with SCD showed that nutritional SPD was associated with a positive effect on memory performance (Wirth et al., 2018). Contrastingly, in another 12-month randomized clinical trial, long-term SPD supplementation in participants with SCD did not modify memory performance and biomarkers compared with placebo (Wirth et al., 2019). Additionally, Joaquim et al. (2019) monitored their study participants for 4 years and found that SPD levels were lower in both patient groups Alzheimer's disease (AD; MCI) than in healthy controls. Graham et al. (2015) showed, through untargeted metabolomic analysis of human plasma, that polyamine metabolism was disrupted in patients with MCI.

Our results confirm that higher baseline serum SPD levels are associated with lower MCI prevalence and incidence, especially in males, and that subgrouping of participants into under 60 and over 60 years. The possible mechanism underpinning this association could be that SPD induces autophagy and exerts additional and potentially autophagy-independent metabolic and transcriptional effects *in vivo* (Madeo et al., 2018). However, cross-sectional analyses revealed a non-linear relationship between SPD and the risk of MCI, i.e., at very high SPD levels, the risk of MCI is elevated. We speculate that the elevated serum SPD levels in the MCI population are a compensatory effect in a pathological state. The geroprotective effects of SPD influence lifespan extension in a hormetic dose-dependent manner (Calabrese et al., 2020). In this hormesis scenario, a high dose of natural compounds is detrimental, because it inhibits antioxidant stress response pathways. The longitudinal study did not reveal a significant non-linear relationship of SPD with MCI. This finding is attributable to the small sample size ($N = 888$) of the longitudinal study and the high failure rate in conducting follow-up. There may be a certain loss to follow-up bias, thereby emphasizing the need for further examination using larger sample sizes.

Compared with previous studies, this study has several strengths. First, unlike previous clinical studies that included dozens of patients, we explore the relationship between serum SPD levels and MCI in a relatively large sample size ($N = 3,774$) of the general population for the first time. Second, there are three main sources of SPD in humans: cellular metabolism; oral absorption from dietary sources; or commensal gut bacteria (Madeo et al., 2018). Instead of assessing dietary SPD intake alone, we assessed overall SPD levels in the body to account for all SPD sources. Simultaneously, the measurement of SPD in serum can avoid the recall bias caused by the dietary assessment scale.

This study, however, also has inevitable limitations. First, we lacked an assessment of dietary SPD intake, which may

affect the *in vivo* SPD level. Therefore, we could not establish a correspondence between serum SPD levels and dietary SPD intake. Second, we only measured the level of SPD once. Dynamically observing the changes in SPD in the blood may help to better identify its relationship with MCI over a time-course. Third, we exclusively examined the Chinese rural population, which may limit generalizability. The dietary culture of different populations differs and SPD is affected by diet (Madeo et al., 2020) and intestinal flora (Ramos-Molina et al., 2019). Therefore, the verification of the diverse population is meaningful.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the procedures followed under the ethical standards of the responsible committee on human experimentation of China Medical University ([2018]083). The patients/participants provided their written informed consent to participate in this study.

Author contributions

LZ and ZS designed the research. JX wrote the manuscript. QZ and FX provided essential reagents or provided essential materials. RZ, RL, and ZY conducted the research. YM performed statistical analysis. LZ was responsible for formulating all the sections of the manuscript. All authors contributed to the article and approved the submitted version.

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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

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Continuous theta burst stimulation over left supplementary motor area facilitates auditory-vocal integration in individuals with Parkinson's disease

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Accumulating evidence suggests that impairment in auditory-vocal integration characterized by abnormally enhanced vocal compensations for auditory feedback perturbations contributes to hypokinetic dysarthria in Parkinson's disease (PD). However, treatment of this abnormality remains a challenge. The present study examined whether abnormalities in auditory-motor integration for vocal pitch regulation in PD can be modulated by neuronavigated continuous theta burst stimulation (c-TBS) over the left supplementary motor area (SMA). After receiving active or sham c-TBS over left SMA, 16 individuals with PD vocalized vowel sounds while hearing their own voice unexpectedly pitch-shifted two semitones upward or downward. A group of pairwise-matched healthy participants was recruited as controls. Their vocal responses and event-related potentials (ERPs) were measured and compared across the conditions. The results showed that applying c-TBS over left SMA led to smaller vocal responses paralleled by smaller P1 and P2 responses and larger N1 responses in individuals with PD. Major neural generators of reduced P2 responses were located in the right inferior and medial frontal gyrus, pre- and post-central gyrus, and insula. Moreover, suppressed vocal compensations were predicted by reduced P2 amplitudes and enhanced N1 amplitudes. Notably, abnormally enhanced vocal and P2 responses in individuals with PD were normalized by c-TBS over left SMA when compared to healthy controls. Our results provide the first

causal evidence that abnormalities in auditory-motor control of vocal pitch production in PD can be modulated by c-TBS over left SMA, suggesting that it may be a promising non-invasive treatment for speech motor disorders in PD.

KEYWORDS

Parkinson's disease, auditory feedback, vocal motor control, continuous theta burst stimulation, supplementary motor area

Introduction

One prominent clinical feature of idiopathic Parkinson's disease (PD) is hypokinetic dysarthria, which is characterized by a reduction in speech volume and pitch fluctuation, inconsistent rates of speech, and imprecise articulation (Duffy, 2005). These abnormalities in speech production occur in individuals with early-stage PD and deteriorate as the disease progresses (Rusz et al., 2013; Moreau and Pinto, 2019). Approximately, 70–90% of individuals with PD have speech motor disorders that limit their communication, social participation, and quality of life (Sapir et al., 2008). However, treatment of PD dysarthria remains a challenge. Despite the remarkable positive effects of pharmacological and surgical interventions on motor limb symptoms of PD, the effects of these treatments on PD dysarthria are commonly more deleterious than they are beneficial (Skodda et al., 2009). The Lee Silverman Voice Treatment (LSVT® LOUD), a behavioral speech therapy designed for the treatment of PD hypophonia, has been shown to produce immediate and long-term (12–24 months) improvement in vocal loudness, pitch variability, and speech intelligibility (Ramig et al., 2001; Sapir et al., 2007). The application of this treatment, however, is limited by high-effort and intensive vocal training that cause many patients to discontinue treatment. Therefore, the development of other effective speech therapies for PD dysarthria remains an important goal.

Repetitive transcranial magnetic stimulation (rTMS) has emerged as an important tool in the experimental treatment of various psychiatric and neurological disorders by non-invasively modulating brain activity to change behaviors (Hallett, 2007). It is generally believed that high-frequency rTMS applied over the target site increases the excitability of cortical neurons, whereas low-frequency rTMS decreases it (Pascual-Leone et al., 1994; Chen and Seitz, 2001), although this relationship may vary as a function of stimulation intensity and individual variability (Fitzgerald et al., 2006; Lopez-Alonso et al., 2014). One meta-analysis showed that high-frequency rTMS over the primary motor cortex (M1) or low-frequency rTMS over the dorsolateral prefrontal cortex (DLPFC) produced moderate improvements in PD motor disorders (Chou et al., 2015). In contrast, studies investigating the efficacy of rTMS for PD dysarthria have found conflicting results. For example, a single session of high-frequency rTMS over the primary orofacial sensorimotor area (SM1) led to improved vocal pitch and loudness, tongue movement, and voice quality in individuals with PD (Dias et al., 2006; Eliasova et al., 2013), whereas high-frequency rTMS over the left DLPFC and left M1 hand area failed to do so (Dias et al., 2006; Hartelius et al., 2010; Eliasova et al., 2013). Brabenec et al. (2019) found that, following a single session of low-frequency rTMS over the right superior temporal gyrus (STG), individuals with PD exhibited increased variability of the second formant that was predicted by enhanced right STG activation during sentence reading. However, beneficial effects were not found when they received high-frequency rTMS over the right STG or SM1. Brabenec et al. (2021) subsequently found that following 10 sessions of low-frequency rTMS over the right STG, individuals with PD exhibited long-term improvement (2–10 weeks) in their phonetics score of Dysarthric Profile that was correlated with resting-state STG-SM1 functional connectivity. Therefore, there is mixed evidence for the benefits of TMS intervention for PD dysarthria.

Among several possible resources of the discrepancies across studies investigating the efficacy of TMS for PD dysarthria are choice of stimulation protocol and assessment of treatment outcomes. High-frequency rTMS has been the most frequent protocol used to increase cortical excitability of the DLPFC, SM1, STG, and M1 for the treatment of PD dysarthria (Dias et al., 2006; Hartelius et al., 2010; Eliasova et al., 2013; Brabenec et al., 2019). A series of neuroimaging studies on individuals with PD, however, have shown an overactivation of the DLPFC, premotor cortex (PMC), supplementary motor area (SMA), and insula during speech production (Liotti et al., 2003; Pinto et al., 2004; Arnold et al., 2014) and enhanced cortical event-related potential (ERP) P2 responses to voice pitch perturbations that were source-localized in the left STG, inferior parietal lobule (IPL), inferior frontal gyrus (IFG), and PMC (Huang et al., 2016). It is therefore plausible that PD dysarthria may result from hyperactivity in the cortical speech motor networks, and thus inhibiting, rather than enhancing, cortical excitability of those regions may reduce this hyperactivity and restore normal levels of brain activation to produce beneficial effects. This

hypothesis is in line with the findings of improved articulatory functions in individuals with PD following low-frequency but not high-frequency rTMS over the right STG (Brabenec et al., 2019). On the other hand, acoustic (e.g., fundamental frequency or f_o, intensity, and formant frequency) and/or perceptual (e.g., phonetics score and speech intelligibility) analyses of PD speech were generally used to evaluate the outcome of TMS intervention (Dias et al., 2006; Eliasova et al., 2013; Brabenec et al., 2019, 2021). These speech characteristics, however, reflect a broad range of mental processes, including voluntary attempts to compensate for the symptoms of PD. As mentioned, abnormalities in the integration of auditory feedback with vocal motor control in PD, characterized by overcompensation for voice pitch and loudness perturbations (Liu et al., 2012; Chen et al., 2013; Huang et al., 2016; Mollaei et al., 2016), have been regarded as significant contributors to PD dysarthria (Sapir, 2014). Thus, an examination of the neurobehavioral correlates that support auditory-motor control of vocal production may uncover the effects of TMS intervention on PD dysarthria from the perspective of sensorimotor integration.

In the present study, we examined whether and, if so, how abnormalities in auditory-vocal integration in individuals with PD can be modulated by neuronavigated continuous theta burst stimulation (c-TBS) over the left SMA. As a specific form of rTMS protocol, c-TBS inhibits the cortical excitability for up to 60 min after less than 1-min stimulation (Huang et al., 2005). The left SMA was chosen as the stimulation target in the present study because it is reciprocally connected with the laryngeal motor cortex for vocal motor command execution (Simonyan and Horwitz, 2011) and plays a central role in the initiation, monitoring, and timing control of speech production (Tourville and Guenther, 2011; Hertrich et al., 2016). Also, the left SMA has been identified as an important motor component of the speech monitoring network (Riecker et al., 2005) and to be active when healthy individuals compensate for perturbations in voice auditory feedback (Zarate and Zatorre, 2008; Behroozmand et al., 2015). Lesions in this region result in speech motor disorders, such as impaired involuntary or spontaneous vocalization and acquired dysfluencies (Jonas, 1981; Ziegler et al., 1997). Moreover, individuals with PD have shown hyperactivity in the SMA during speech production (Liotti et al., 2003; Pinto et al., 2004; Arnold et al., 2014), and a reduction of SMA activation was accompanied by improved speech scores of the UPDRS as a result of subthalamic nucleus (STN) stimulation (Pinto et al., 2004). Thus, c-TBS over the left SMA of individuals with PD may lead to a functional normalization of the speech motor systems that produce beneficial effects on their auditory-motor control of vocal production.

The intervention outcome was assessed using the frequency-altered feedback (FAF) paradigm (Burnett et al., 1998), which involves participants hearing their voice f_o unexpectedly shifted upward or downward during vocal production. We evaluated the vocal and ERP responses (P1-N1-P2) to pitch perturbations in auditory feedback after applying active or sham c-TBS over the left SMA. Individuals with PD have been found to show larger vocal compensations for pitch perturbations and/or greater ERP P2 responses relative to healthy controls (Liu et al., 2012; Chen et al., 2013; Huang et al., 2016; Mollaei et al., 2016; Li et al., 2021). This vocal overcompensation, however, returned to normal when they vocalized the sounds with external auditory cueing (Huang et al., 2019) or received voice treatment with LSVT® LOUD (Li et al., 2021). Therefore, we hypothesized that individuals with PD following c-TBS over the left SMA would likewise exhibit reduced vocal and cortical ERP responses to pitch perturbations that reflect beneficial effects on their abnormalities in auditory-vocal integration.

Materials and methods

Subjects

A group of 16 Chinese-speaking adults (6 women and 10 men; mean age: 64.88 ± 9.88 years) diagnosed as idiopathic PD according to the United Kingdom Parkinson's disease Society Brain Bank (Hughes et al., 1992) participated in the present study (see details in **Table 1**). They were included in the present study based on the following criteria: no contraindication for magnetic resonance imaging (MRI) and TMS, no dementia or psychiatric abnormalities, no neurological diseases other than PD, no experience with musical training, and no history of neurosurgical treatment or speech therapy. Individuals with PD participated in the experiment within 1–2 h after taking their regular antiparkinsonian medication. They did not show any wearing-off phenomena and/or L-dopa-induced dyskinesias. A group of 16 neurologically normal participants was recruited as healthy controls and pairwise-matched with individuals with PD on age and sex (6 women and 10 men; mean age: 64.25 ± 6.95 years; $t = 0.207$, d.f. = 30, $p = 0.837$). All participants passed a binaural hearing screening at thresholds of 40 dB hearing level or less for 500, 1,000, 2,000, and 4,000 Hz. The research protocol was approved by the Institutional Review Board of The First Affiliated Hospital of Sun Yat-sen University, and all participants provided their written informed consent.

Magnetic resonance imaging data acquisition

Prior to the c-TBS experiment, high-resolution anatomical images were acquired from all participants using a 3T MRI scanner (Siemens, Germany) to precisely define the stimulation target. A T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence was used during the scanning with the following parameters: repetition time (TR) = 2,000 ms,

TABLE 1 Clinical and demographic data of PD patients.

ID	Gender	Age (ys)	Disease duration (ys)	H-Y stage	UPDRS-II	UPDRS-III	MMSE
1	M	73	17	2.5	12	18	27
2	F	68	7	1.5	15	26	30
3	F	64	4	2	11	16	27
4	M	53	2	1.5	4	23	29
5	M	63	10	3	15	31	30
6	F	73	5	1.5	6	11	30
7	M	63	11	3	22	26	24
8	M	42	2	1.5	5	9	30
9	F	76	3	1.5	11	12	30
10	M	48	12	2.5	17	38	30
11	M	74	8	2	16	28	30
12	F	70	4	2.5	13	30	30
13	F	65	3	1.5	10	21	30
14	M	73	3	2	14	23	30
15	M	61	6	2.5	7	48	26
16	M	72	5	1.5	1	9	29

PD, Parkinson's disease; M, male; F, female; ys, years; H-Y Stage, Hoehn and Yahr stage, UPDRS-II, the Unified Parkinson's Disease Rating Scale part II; UPDRS-III, the Unified Parkinson's Disease Rating Scale part III; MMSE, Mini-Mental Status Examination.

echo time (TE) = 1.76 ms, slice thickness = 0.8 mm, voxel size = 0.8 × 0.8 × 0.8 mm^3, field of view (FOV) = 260 × 260 mm^2, and 224 sagittal slices.

Neuronavigated transcranial magnetic stimulation

Magnetic stimulation was administered using a CCY-I TMS instrument (YIRUIDE Co., Wuhan, China) equipped with a 7-cm-outer-diameter figure-of-eight coil. Prior to the c-TBS intervention, the left M1 was stimulated with single-pulse TMS to determine the resting motor threshold (RMT) by recording the motor evoked potentials (MEPs) of each individual from the right first dorsal interosseous (FDI) muscles. The RMT was defined as the lowest stimulus intensity sufficient to elicit an MEP $\geq$ 50 μV in 5 out of 10 consecutive trials in the resting right FDI (Groppa et al., 2012). A standard c-TBS protocol that consisted of 600 pulses in a theta burst pattern (bursts of 3 pulses at 50 Hz repeated every 200 ms; Huang et al., 2005) was applied over the left SMA at 80% of RMT (Grossheinrich et al., 2009). The location of the left SMA (MNI coordinates: x = −3, y = −2, and z = 58; Bolzoni et al., 2015) was determined by loading individual anatomical MRI data into a neuronavigation software (Visor 2.0, ANT Neuro, Netherlands) with a Polaris Spectra motion tracking system (NDI, Canada). These coordinates were slightly modified based on individual brain anatomical landmarks to ensure correct positioning over left SMA. In order to rule out any spread of current into the contralateral SMA when TMS was applied over one SMA, the coil was orientated medio-laterally with the handle pointing toward the right hemisphere to stimulate the left SMA (White et al., 2013). Active c-TBS was delivered by placing the coil closely tangential to the skull surface. Sham stimulation was delivered with the coil 90° tilted away from the target with one wing of the coil touching the scalp. The order of active or sham c-TBS over the left SMA was counterbalanced across all participants, with active and sham sessions occurring on separate days at least 48 h apart (Brabenec et al., 2019). Healthy participants served as controls to determine the degree of impairment and improvement of auditory-vocal integration in individuals with PD and thus did not receive active or sham c-TBS over the left SMA.

Experimental design

One FAF-based vocal production experiment began immediately after applying active or sham c-TBS over the left SMA to individuals with PD. Healthy controls performed the same experiment as well. All participants were instructed to produce the vowel /u/ for about 2–3 s while hearing their voice pseudo-randomly pitch-shifted upward or downward twice by 200 cents (200 ms duration; 100 cents = 1 semitone). The first pitch perturbation occurred after a random delay of 1,500–2,500 ms relative to the vocal onset, and the second stimulus was presented after an inter-stimulus interval of 700–1,000 ms. All participants were required to take a break of 2–3 s between consecutive vocalizations to avoid vocal fatigue. Each participant produced 100 consecutive vocalizations, leading to 100 trials for + 200 cents perturbations and 100 trials for −200 cents perturbations. The vocal production experiment

was conducted with the same experimental parameters after individuals with PD received active or sham c-TBS.

Apparatus

The vocal production experiment was conducted in a sound-attenuated room. First, the voice signals were transduced through a dynamic microphone (DM2200, Takstar Inc.) and sent to an Eventide Eclipse Harmonizer through a MOTU Ultralite Mk3 Firewire audio interface. A MIDI software program (Max/MSP v.5.0 by Cycling 74) was developed to control the Eventide Eclipse Harmonizer to pitch-shift the voice signals with preset parameters. Meanwhile, transistor-transistor logic (TTL) control pulses were generated by this program to mark the onset of each pitch perturbation. Finally, the pitch-shifted voice signals were amplified by an ICON Neo Amp headphone amplifier and played back to participants through inserted earphones (ER-1, Etymotic Research Inc.). The original and pitch-shifted voice signals as well as the TTL control pulses were digitized by a PowerLab A/D converter (model ML880, AD Instruments) and recorded at 10 kHz using LabChart software (v.7.0, AD Instruments).

Simultaneously, the EEG signals were scalp-recorded using a 64-electrode Geodesic Sensor Net (Electrical Geodesics Inc.), amplified by a high-input impedance NetAmps 300 amplifier (Electrical Geodesics Inc.), and recorded at a sampling frequency of 1 kHz using NetStation software (v.4.5, Electrical Geodesics Inc.). Since the amplifier accepts scalp-electrode impedances up to 40–60 kΩ, the impedance levels of individual sensors were kept below 50 kΩ throughout the recording (Ferree et al., 2001). The EEG signals across all channels were referenced to the vertex (Cz) during the recording (Ferree et al., 2001). An experimental DIN synch cable sent the TTL control pulses to the EEG recording system for the synchronization of the voice and EEG signals.

Data analyses

The behavioral measurement, including the peak magnitude and peak latency of vocal responses to pitch perturbations, was performed in a custom-developed IGOR PRO software program (v.6.0 by Wavemetrics Inc.) that has been previously described in detail (Huang et al., 2019). In brief, the voice f_o contours in Hertz were extracted and converted to the cent scale using the following formula: cents = $100 \times [12 \times \log_2(f_o/\text{reference})]$ [reference = 195.997 Hz (G3)]. They were then segmented into epochs ranging from −200 to +700 ms relative to the perturbation onset and visually inspected for trial-by-trial artifact rejection. Overall, 81% of the individual trials were regarded as artifact-free trials. The trials were averaged and baseline-corrected (−200 to 0 ms) to generate an overall vocal response for each condition. The magnitude and latency of a vocal response were separately measured as the maximum or minimum value in cents and the corresponding time in milliseconds when the voice f_o contour reached its peak value.

The offline analyses of EEG signals were performed using NetStation software. They were band-pass filtered between 1 and 20 Hz, segmented into epochs using a window of −200 to +500 ms relative to the perturbation onset, and submitted to an artifact detection procedure to exclude those trials with voltage values that exceeded ± 55 μv of the moving average over an 80-ms window from further analysis. A trial-by-trial visual inspection was additionally performed to ensure that bad trials were appropriately rejected. Individual electrodes that contained artifacts in more than 20% of the epochs were rejected, and files that contained more than 10 bad channels were marked bad. Finally, artifact-free individual trials were re-referenced to the average of the electrodes on each mastoid, averaged, and baseline-corrected (−200 to 0 ms) to generate an overall ERP response to pitch perturbations. Since the cortical P1, N1, and P2 responses to pitch perturbations were prominently pronounced in the frontal and central regions (Behroozmand et al., 2009; Scheerer et al., 2013), we chose 24 electrodes in three regions of interest (ROI) for statistical analysis: frontal area, including AF3, AFz, AF4, F5, F3, F1, Fz, F2, F4, and F6; fronto-central area, including FC5, FC3, FC1, FCz, FC2, FC4, and FC6; central area, including C5, C3, C1, Cz, C2, C4, and C6. The amplitudes and latencies of the P1, N1, and P2 components were extracted from the averaged ERPs for each ROI.

Source localization

The sLORETA software[1] (Fuchs et al., 2002) was used to localize the neural generators of the P1, N1, and P2 responses that differed between active and sham stimulation for individuals with PD. This method partitions the intracerebral volume into 6,239 cortical gray matter voxels at a 5-mm spatial resolution and calculates the standardized current density in a realistic standardized head model within the MNI152 template (Mazziotta et al., 2001). In the present study, the voxel-based sLORETA images were computed based on the averaged ERPs within 5 ms time windows centered at the maximal global field power peaks in the P1, N1, and P2 time windows and compared between active and sham stimulations using voxel-wise randomization tests with 10,000 permutations. Multiple comparisons were corrected at a whole-brain level based on the statistical non-parametric mapping. The voxels with significant differences (for corrected $p < 0.05$) were specified in MNI coordinates and Brodmann areas (BA). The results were

1 http://www.uzh.ch/keyinst/loreta.htm

superimposed on an anatomical template in BrainNet Viewer (Xia et al., 2013).

Statistical analyses

The values of vocal and ERP responses were submitted to SPSS (v.20.0) for statistical analysis. For individuals with PD, the magnitudes and latencies of vocal responses were subjected to two-way RM-ANOVAs, including within-subject factors of perturbation direction (−200 vs. +200 cents) and stimulation session (active vs. sham c-TBS). The amplitudes and latencies of the P1, N1, and P2 responses were subjected to three-way RM-ANOVAs, including within-subject factors of perturbation direction, stimulation session, and electrode site (frontal, fronto-central, and central). In addition, mixed-design ANOVAs were used to compare the differences in the vocal and ERP responses between individuals with PD following active/sham stimulation and healthy controls across the conditions. Subsidiary RM-ANOVAs were performed if any higher-order interactions between these variables were significant. Bonferroni correction was used for multiple comparisons in *post hoc* analyses. Probability values for multiple degrees of freedom were corrected using the Greenhouse–Geisser correction factor if the assumption of Mauchly's test of Sphericity was violated. In addition, effect sizes indexed by partial η^2 were calculated to quantify the proportion of variance.

Results

Behavioral findings

Figure 1 shows the grand-averaged voice f_0 responses to pitch perturbations of ± 200 cents for individuals with PD following active and sham c-TBS over the left SMA and healthy controls. A two-way RM-ANOVA conducted on the peak magnitudes of vocal responses in individuals with PD revealed a significant main effect of the stimulation session [$F(1, 15) = 17.916$, $p = 0.001$, partial $\eta^2 = 0.544$], showing that active c-TBS over the left SMA led to smaller vocal compensations than sham stimulation (see Figure 1C). The main effect of perturbation direction [$F(1, 15) = 0.034$, $p = 0.857$] and its interaction with stimulation session [$F(1, 15) = 0.365$, $p = 0.555$], however, did not reach significance. Regarding the peak times of vocal responses, there were no significant main effects of stimulation session [$F(1, 15) = 1.960$, $p = 0.182$] and perturbation direction [$F(1, 15) = 1.822$, $p = 0.197$] (see Figure 1D). Their interaction was not significant either [$F(1, 15) = 0.001$, $p = 0.975$].

A two-way mixed-design ANOVA showed significantly larger magnitudes of vocal responses for individuals with PD receiving sham stimulation than for healthy controls [$F(1, 30) = 7.540$, $p = 0.010$, partial $\eta^2 = 0.201$] (see Figure 1C). The main effect of perturbation direction [$F(1, 30) = 0.292$, $p = 0.593$] and its interaction with group [$F(1, 30) = 0.338$, $p = 0.565$] were not significant. However, after receiving active c-TBS over the left SMA, individuals with PD were not significantly different from the healthy controls in the magnitudes of vocal responses [$F(1, 30) = 0.331$, $p = 0.569$]. The main effect of perturbation direction [$F(1, 30) = 0.165$, $p = 0.688$] and its interaction with group [$F(1, 30) = 0.140$, $p = 0.711$] were not significant.

Regarding the peak times of vocal responses, there was no significant difference between individuals with PD receiving sham stimulation and healthy controls [$F(1, 30) = 1.290$, $p = 0.265$]. The main effect of perturbation direction [$F(1, 30) = 0.001$, $p = 0.980$] and its interaction with group [$F(1, 30) = 3.643$, $p = 0.066$] did not reach significance. Similarly, the peak times of vocal responses were not significantly different between individuals with PD receiving active c-TBS over the left SMA and healthy controls [$F(1, 30) = 0.006$, $p = 0.940$] and between upward and downward perturbations [$F(1, 30) = 0.015$, $p = 0.904$]. The interaction between these two factors was not significant [$F(1, 30) = 2.382$, $p = 0.133$].

Event-related potential findings

Figure 2 shows the grand-averaged ERPs and topographical distributions, as well as the violin plots of the P1, N1, and P2 responses to pitch perturbations across the group and stimulation session. A three-way RM-ANOVA conducted on the P1 amplitudes in individuals with PD revealed a significant main effect of stimulation session [$F(1, 15) = 11.679$, $p = 0.004$, partial $\eta^2 = 0.438$], where c-TBS over the left SMA led to smaller P1 responses than sham stimulation (see Figure 2A). Also, a significant main effect of electrode site [$F(2, 30) = 9.269$, $p = 0.006$, partial $\eta^2 = 0.382$] led to smaller P1 responses at the central electrodes as compared to the frontal ($p = 0.024$) and fronto-central electrodes ($p = 0.010$). However, the main effect of perturbation direction [$F(1, 15) = 1.738$, $p = 0.207$] and interactions between any of the three factors ($p > 0.06$) were not significant. Regarding the P1 latencies, individuals with PD exhibited no significant main effects of stimulation session [$F(1, 15) = 3.055$, $p = 0.101$], perturbation direction [$F(1, 15) = 0.175$, $p = 0.682$], and electrode site [$F(2, 30) = 0.121$, $p = 0.787$] (see Figure 2B). Their interactions were also not significant ($p > 0.2$).

A three-way mixed-design ANOVA showed no significant differences in the P1 amplitudes between individuals with PD receiving sham stimulation and healthy controls [$F(1, 30) = 3.659$, $p = 0.066$]. However, there was a significant main effect of the electrode site [$F(2, 58) = 12.448$, $p = 0.001$, partial $\eta^2 = 0.300$], showing larger P1 amplitudes at the frontal electrodes than at the fronto-central ($p = 0.020$) and central electrodes ($p = 0.005$). Also, there were larger P1 amplitudes

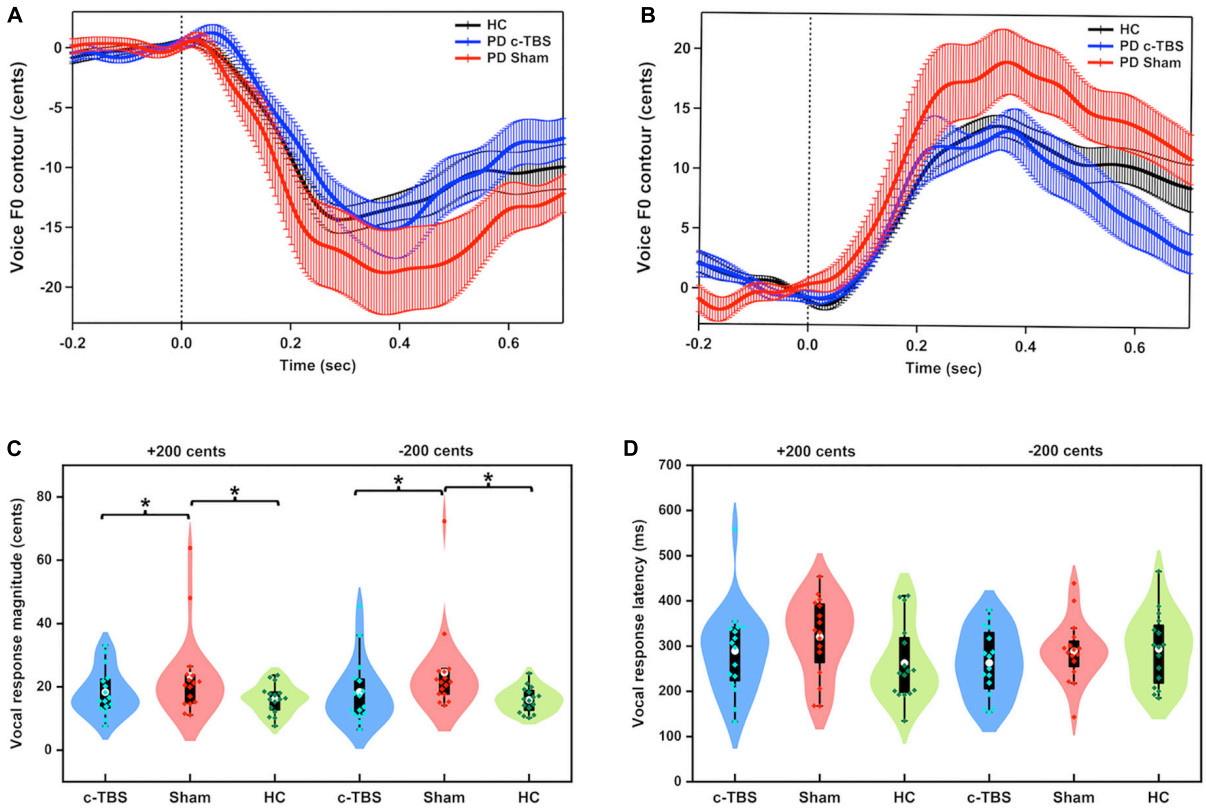

FIGURE 1
(A,B) Grand-averaged voice f_o contours in response to pitch perturbations of ± 200 cents in individuals with PD following active (blue solid lines) and sham (red solid lines) c-TBS over the left SMA and healthy controls (black solid lines). Vertical bars across the contours indicate the standard errors of the mean vocal responses. Vertical dashed lines indicate the onset of the pitch perturbation. **(C,D)** Violin plots of the magnitudes and latencies of vocal responses to ± 200 cents in individuals with PD following active (blue) and sham stimulation (red) and healthy controls (green). The shape of the violin shows the kernel density estimate of the data. The white dots and box plots represent the medians and range from the first to third quartiles of the data sets. The blue, red, and green dots represent the individual vocal responses to pitch perturbations. The asterisks indicate significant differences across the conditions.

at the fronto-central electrodes that at the central electrodes ($p = 0.006$). The main effect of perturbation direction [$F(1, 30) = 0.219$, $p = 0.643$] and the interactions between any of the three factors were not significant ($p > 0.07$). Regarding the P1 latencies, there were no significant main effects of group [$F(1, 30) = 1.769$, $p = 0.194$], perturbation direction [$F(1, 30) = 0.576$, $p = 0.454$], and electrode site [$F(2, 58) = 0.683$, $p = 0.445$]. Their interactions were not significant either ($p > 0.5$).

As well, no significant differences in the P1 amplitudes were found between individuals with PD following c-TBS over the left SMA and healthy controls [$F(1, 30) = 0.105$, $p = 0.748$] and between upward and downward perturbations [$F(1, 30) = 0.029$, $p = 0.867$]. There was a significant main effect of the electrode site [$F(2, 58) = 20.046$, $p < 0.001$, partial $\eta^2 = 0.401$], showing smaller P1 amplitudes at the central electrodes than at the frontal ($p < 0.001$) and fronto-central electrodes ($p < 0.001$). The interactions between any of the three factors were not significant ($p > 0.1$). Regarding the P1 latencies, the main effects of group [$F(1, 30) = 2.902$, $p = 0.099$], perturbation direction [$F(1, 30) = 0.849$, $p = 0.364$], and electrode site [$F(2, 58) = 0.173$, $p = 0.742$], as well as their interactions, ($p > 0.6$) were not significant.

A three-way RM-ANOVA conducted on the N1 amplitudes in individuals with PD showed that c-TBS over the left SMA led to significantly more negative N1 responses than sham stimulation [$F(1, 15) = 8.115$, $p = 0.012$, partial $\eta^2 = 0.351$] (see Figure 2C). A significant main effect of the electrode site [$F(2, 30) = 16.939$, $p < 0.001$, partial $\eta^2 = 0.530$] was also found, showing less negative N1 responses at the frontal electrodes when compared to the fronto-central ($p < 0.001$) and central electrodes ($p = 0.005$). However, the main effect of perturbation direction [$F(1, 15) = 1.443$, $p = 0.248$] and interactions between any of the three factors ($p > 0.09$) were not significant. In addition, the N1 latencies did not vary significantly as a function of stimulation session [$F(1, 15) = 0.145$, $p = 0.709$], perturbation direction [$F(1, 15) = 1.240$, $p = 0.283$], and electrode site [$F(2, 30) = 1.553$, $p = 0.233$] (see Figure 2D). Their interactions were also not significant ($p > 0.2$).

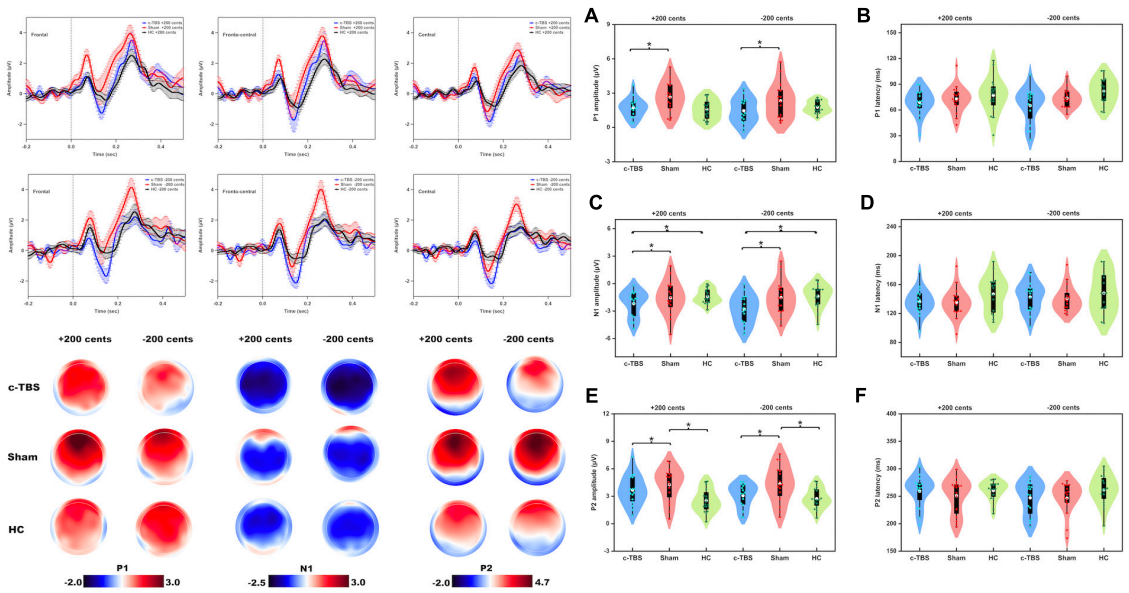

FIGURE 2
Top left: Grand-averaged ERPs to pitch perturbations of ± 200 cents in the frontal, fronto-central, and central regions in individuals with PD following active (blue solid lines) and sham (red solid lines) c-TBS over the left SMA and healthy controls (black solid lines). Vertical bars across the contours indicate the standard errors of the mean ERPs. Vertical dashed lines indicate the onset of the pitch perturbation. *Bottom left*: Topographical distribution maps of the P1, N1, and P2 amplitudes in responses to pitch perturbations of ± 200 cents in individuals with PD following active and sham stimulation and healthy controls. *Right Panel:* Violin plots of the amplitudes and latencies of the P1 **(A,B)**, N1 **(C,D)**, and P2 **(E,F)** responses to pitch perturbations of ± 200 cents in individuals with PD following active (blue) and sham (red) stimulation and healthy controls (green). The white dots and box plots represent the medians and range from the first to third quartiles of the data sets. The blue, red, and green dots represent the individual ERP responses to pitch perturbations. The asterisks indicate significant differences across the conditions.

A three-way mixed-design ANOVA revealed no significant differences in the N1 amplitudes between individuals with PD receiving sham stimulation and healthy controls [$F(1, 30) = 0.082$, $p = 0.776$] and between upward and downward pitch perturbations [$F(1, 30) = 0.018$, $p = 0.893$]. There was a significant main effect of the electrode site [$F(2, 58) = 22.425$, $p < 0.001$, partial $\eta^2 = 0.428$], showing more negative N1 responses at the frontal electrodes when compared to the fronto-central ($p < 0.001$) and central electrodes ($p = 0.001$). The interactions between any of the three factors were not significant ($p > 0.05$). Regarding the N1 latencies, there were no significant main effects of group [$F(1, 30) = 1.780$, $p = 0.192$], perturbation direction [$F(1, 30) = 0.539$, $p = 0.469$], and electrode site [$F(2, 58) = 0.439$, $p = 0.624$], as well as their interactions ($p > 0.1$).

In contrast, individuals with PD receiving c-TBS over the left SMA produced significantly more negative N1 amplitudes than healthy controls [$F(1, 30) = 7.067$, $p = 0.012$, partial $\eta^2 = 0.191$] (see Figure 2C). Also, a significant main effect of the electrode site [$F(2, 58) = 16.335$, $p < 0.001$, partial $\eta^2 = 0.353$] led to more negative N1 responses at the frontal electrodes when compared to the fronto-central ($p < 0.001$) and central electrodes ($p = 0.010$). The main effect of perturbation direction [$F(1, 30) = 1.657$, $p = 0.208$] and interactions between any of the three factors were not significant ($p > 0.1$). Regarding the N1 latencies, there were no significant main effects of group [$F(1, 30) = 1.162$, $p = 0.290$], perturbation direction [$F(1, 30) = 0.989$, $p = 0.328$], and electrode site [$F(2, 58) = 1.614$, $p = 0.209$]. Their interactions were also not significant ($p > 0.2$).

A three-way RM-ANOVA conducted on the P2 amplitudes in individuals with PD showed that c-TBS over the left SMA led to significantly smaller P2 responses than sham stimulation [$F(1, 15) = 13.292$, $p = 0.002$, partial $\eta^2 = 0.470$] (see Figure 2E). There was also a significant main effect of the electrode site [$F(2, 30) = 22.031$, $p < 0.001$, partial $\eta^2 = 0.595$], which was driven by smaller P2 responses at the central electrodes as compared to the frontal ($p = 0.001$) and fronto-central electrodes ($p < 0.001$). The main effect of perturbation direction [$F(1, 15) = 0.993$, $p = 0.335$] and the interactions between any of the three factors ($p > 0.1$) were not significant. Regarding the P2 latencies, the main effects of stimulation condition [$F(1, 15) = 0.850$, $p = 0.371$], perturbation direction [$F(1, 15) = 1.283$, $p = 0.275$], and electrode site [$F(2, 30) = 0.504$, $p = 0.514$] as well as their interactions ($p > 0.1$) were not significant (see Figure 2F).

A three-way mixed-design ANOVA showed that individuals with PD receiving sham stimulation produced larger P2 responses than healthy controls [$F(1, 30) = 9.797$, $p = 0.004$, partial $\eta^2 = 0.246$] (see Figure 2E). There was also a significant main effect of the electrode site [$F(2, 58) = 30.140$, $p < 0.001$, partial $\eta^2 = 0.501$], showing larger P2 amplitudes at the central electrodes as compared to the frontal ($p < 0.001$)

and fronto-central ($p < 0.001$) electrodes. The main effect of perturbation direction [$F(1, 30) = 0.557$, $p = 0.461$] and the interactions between any of the three factors were not significant ($p > 0.05$). Regarding the P2 latencies, there were no significant main effects of group [$F(1, 30) = 2.619$, $p = 0.116$], perturbation direction [$F(1, 30) = 0.076$, $p = 0.784$], and electrode site [$F(2, 58) = 0.452$, $p = 0.6590$]. Their interactions were not significant ($p > 0.1$).

In contrast, individuals with PD receiving c-TBS over the left SMA and healthy controls did not show significant differences in the P2 amplitudes [$F(1, 30) = 3.183$, $p = 0.085$]. There was a significant main effect of the electrode site [$F(2, 58) = 38.215$, $p < 0.001$, partial $\eta^2 = 0.560$], showing smaller P2 amplitudes at the central electrodes than at the frontal ($p < 0.001$) and fronto-central electrodes ($p < 0.001$). Also, larger P2 amplitudes at the frontal electrodes were found when compared to the fronto-central electrodes ($p = 0.014$). The main effect of perturbation direction [$F(1, 30) = 0.652$, $p = 0.426$] and the interactions between any of the three factors were not significant ($p > 0.1$). Regarding the P2 latencies, there were no significant main effects of group [$F(1, 30) = 0.978$, $p = 0.331$], perturbation direction [$F(1, 30) = 1.035$, $p = 0.317$], and electrode site [$F(2, 58) = 0.211$, $p = 0.728$]. Their interactions were not significant ($p > 0.2$).

Individual variability in continuous theta burst stimulation (c-TBS) effects

Figure 3 shows the distribution of left SMA c-TBS effects on the vocal, P1, N1, and P2 responses to pitch perturbations in individuals with PD between active and sham stimulation. Active > Sham represents a decrease of vocal, P1, and P2 responses and an increase of N1 responses, while Sham > Active represents the opposite effects. Of the 32 behavioral/neural responses to upward and downward pitch perturbations produced by 16 individuals with PD, 84% of the vocal responses, 78% of the P1 responses, and 78% of the P2 responses decreased and 72% of the N1 responses increased after active c-TBS over the left SMA, reflecting differences in the direction of c-TBS effects on the neurobehavioral processing of vocal pitch errors. In addition, individual variability for this direction effect was also illustrated by the lines that connected the vocal and ERP responses in the active and sham stimulations across the participants.

Source reconstruction findings

Figure 4 shows estimated current density source maps that display cortical regions where individuals with PD exhibited significantly reduced P2 responses to pitch perturbations in voice auditory feedback following active vs. sham c-TBS over the left SMA. Table 2 lists the anatomical description and the MNI coordinates corresponding to these brain regions. Reduced P2 responses received contributions from a complex network, including the right inferior frontal gyrus (IFG; BA 46/10, $p = 0.0001$), middle frontal gyrus (MFG; BA 46, $p = 0.0009$), precentral gyrus (PrCG; BA 6, $p = 0.0043$), post-central gyrus (PoCG; BA 43/3, $p = 0.0184$), and insula (BA 13; $p = 0.0269$). Although systematic changes in the P1 and N1 amplitudes were found as a result of c-TBS over the left SMA, different levels of current density for these two components did not reach significance and therefore are not illustrated.

Brain–behavior relationship

In order to investigate the relationship between changes in vocal motor behavior and cortical brain activity induced by c-TBS over the left SMA in individuals with PD, regression analyses were performed by correlating the active-sham differences between the magnitudes of vocal responses and the amplitudes of the three ERP components. As shown in Figure 5, the active-sham magnitudes of the vocal responses were significantly correlated with the active-sham amplitudes of the N1 ($r = 0.369$, $p = 0.037$) and P2 ($r = 0.420$, $p = 0.017$) responses. That is, greater suppression of vocal responses was associated with greater enhancement of N1 responses and suppression of P2 responses, suggesting that changes in cortical brain activity induced by c-TBS over the left SMA contributed significantly to normalization of vocal pitch regulation in individuals with PD. However, this correlation was marginally significant in the active-sham differences between the magnitudes of vocal responses and the amplitudes of the P1 responses ($r = 0.339$, $p = 0.058$).

Discussion

The present study investigated whether abnormalities in auditory-vocal integration associated with PD can be modulated by neuronavigated c-TBS over the left SMA. The results showed that individuals with PD exhibited smaller vocal compensations for pitch perturbations paralleled by smaller cortical P1 and P2 responses and larger N1 responses following c-TBS over the left SMA when compared to sham stimulation. Source reconstruction revealed contributions of the right IFG, MFG, PrCG, PoCG, and insula to reduced P2 responses induced by c-TBS over the left SMA. Notably, suppression of vocal compensations was significantly correlated with enhancement of N1 amplitudes and suppression of P2 amplitudes. In addition, as compared to healthy controls, individuals with PD exhibited a normalization of abnormally enhanced vocal and P2 responses to pitch perturbations after receiving c-TBS over the left SMA. These findings provide the first neurobehavioral evidence for the beneficial effects of c-TBS over the left SMA on impaired auditory-vocal integration in PD.

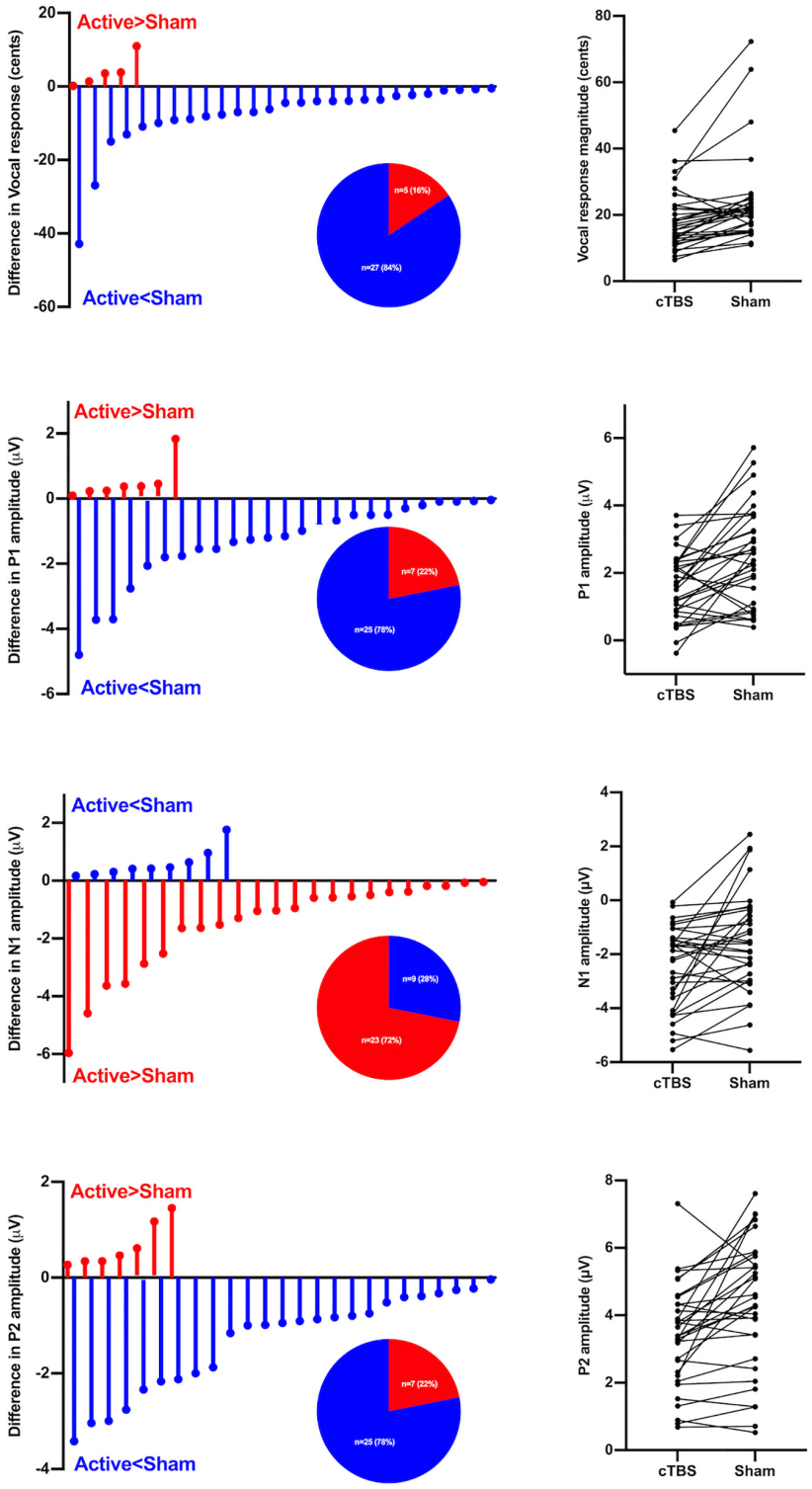

FIGURE 3
Left panel: Individual variability in the direction of left SMA c-TBS effects on vocal pitch regulation in individuals with PD, as reflected by differences in the vocal, P1, N1, and P2 responses to pitch perturbations of ± 200 cents between active and sham conditions. Active > Sham represents a decrease in vocal, P1, and P2 responses and an increase in N1 responses following c-TBS over the left SMA, and Sham > Active represents the opposite effects. The pie charts show the distributions of Active > Sham and Sham > Active responses across the conditions. *Right panel*: Individual vocal, P1, N1, and P2 responses to pitch perturbations of ± 200 cents between active and sham conditions in individuals with PD. Each line represents how an individual subject's vocal or ERP (P1, N1, P2) response under c-TBS over the left SMA compares to that under sham stimulation.

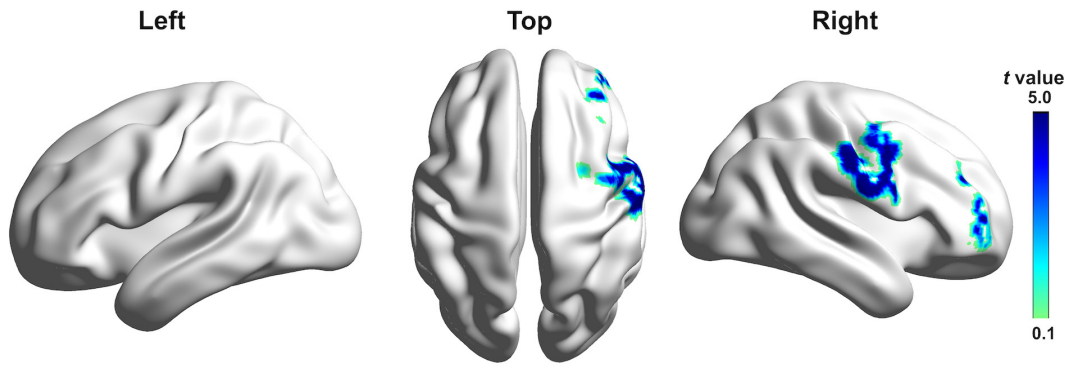

FIGURE 4
Grand-averaged sLORETA-based statistical non-parametric maps comparing the standardized current densities between active and sham c-TBS over the left SMA in the P2 time window. Results are projected onto lateral and top three-dimensional views of a standard anatomical template. Positive *t*-values indicate reduced brain activity caused by active stimulation (corrected $p < 0.05$).

TABLE 2 sLORETA *t*-statistics on log-transformed data.

Condition	BA	Brain region	*t*-value	X	Y	Z	*p*
c-TBS vs. Sham	46/10	Right IFG	−5.472	45	35	15	0.0001
	46	Right MFG	−4.993	45	30	20	0.0009
	6	Right PrCG	−4.610	40	−10	35	0.0043
	43/3	Right PoCG	−4.169	65	−15	30	0.0184
	13	Right Insula	−4.057	50	−25	20	0.0269

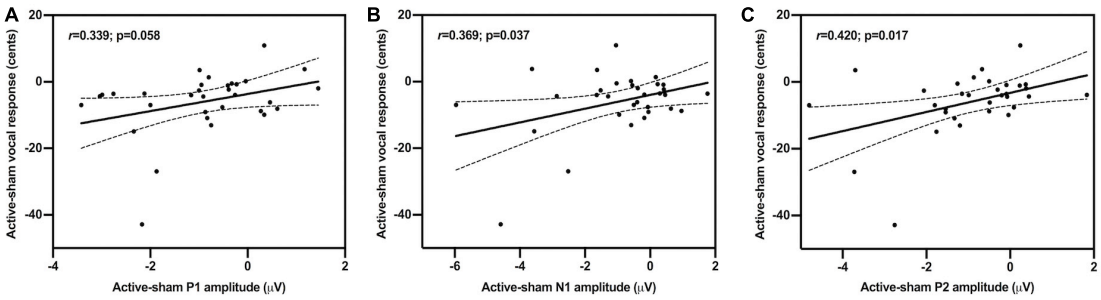

FIGURE 5
Scatter plots illustrating correlations between the active-sham differences in the magnitudes of vocal compensations and the amplitudes of the P1 **(A)**; $r = 0.339$, $p = 0.058$, N1 **(B)**; $r = 0.369$, $p = 0.037$, and P2 **(C)**; $r = 0.420$, $p = 0.017$ responses to pitch perturbations.

Consistent with our hypothesis, applying c-TBS over left SMA in individuals with PD decreased their abnormal vocal responses to pitch perturbations. This is in line with recent findings of decreased vocal compensations for pitch perturbations when individuals with PD vocalized with external auditory cueing (Huang et al., 2019) or received intensive voice treatment with LSVT® LOUD (Li et al., 2021). As well, while replicating earlier reports of abnormally enhanced vocal compensations for pitch perturbations in individuals with PD (Liu et al., 2012; Chen et al., 2013; Huang et al., 2016; Mollaei et al., 2016), the present study found a normalization of this abnormality as a result of c-TBS over their left SMA. Similarly, individuals with PD following LSVT® LOUD produced normalized and reduced vocal compensations that were significantly correlated with their improved vocal loudness during passage reading (Li et al., 2021). These findings suggest that the observed decrease and normalization of vocal compensation in individuals with PD may reflect an improvement of auditory-vocal integration induced by c-TBS over the left SMA that allows them to correctly perceive and appropriately correct mismatches between their intended and actual vocal output.

Moreover, these behavioral effects were paralleled by systematic changes in cortical brain activity in individuals

with PD, as reflected by reduced P1 and P2 responses and enhanced N1 responses to pitch perturbations following c-TBS over the left SMA. Similarly, other PD studies showed that multiple sessions of low-frequency rTMS over the right STG led to enhanced resting-state functional connectivity between the right STG and parahippocampal gyrus (Brabenec et al., 2019) and increased activation of the SM1 and caudate nucleus (Brabenec et al., 2021). These two studies also reported significant correlations between improved speech articulation and enhanced right STG activation during sentence reading (Brabenec et al., 2019) and resting-state STG-SM1 functional connectivity (Brabenec et al., 2021), which is in line with our results showing that reduced vocal compensations were predicted by enhanced N1 responses and reduced P2 responses. These findings provide evidence that low-frequency rTMS or c-TBS over sensory or motor regions can lead to improvement in speech motor skills in PD.

In addition, the present study showed high inter-individual variability in the vocal and ERP responses to pitch perturbations for individuals with PD following active and sham stimulation. Moreover, not all behavioral and neural responses were modulated in the same direction: following c-TBS over the left SMA, 78–84% of vocal, P1, and P2 responses were reduced and 72% of N1 responses were enhanced, while the others showed the opposite pattern (see **Figure 3**). Such inter-individual variability has also been reported in previous empirical and clinical studies that investigated the TMS effects on motor and cognitive behaviors (Lopez-Alonso et al., 2014; Corp et al., 2020; Lin et al., 2022), depending on many factors such as stimulation protocol, brain structure, hormonal levels, and genetic polymorphisms (Polania et al., 2018). Addressing inter-individual variability of TMS effects has crucial implications for improving the efficacy of this non-invasive brain stimulation approach for the treatment of motor speech disorders in PD.

Potential mechanisms of the efficacy of SMA c-TBS

The present study showed systematic changes in the neurobehavioral responses to vocal pitch errors when individuals with PD received active vs. sham c-TBS over the left SMA, highlighting the essential role of this region in vocal motor control. In the DIVA model, the SMA is hypothesized to be a central component of the feedforward control system controlling the initiation of speech motor commands (Tourville and Guenther, 2011). Dysfunctional activation of the SMA has been consistently identified in individuals with PD, particularly showing hyperactivation of this region during speech production (Liotti et al., 2003; Pinto et al., 2004; Arnold et al., 2014). As such, individuals with PD are impaired in the feedforward control of speech production, showing abnormally reduced adaptive responses to predictable voice f_0 and speech F_1 perturbations (Mollaei et al., 2013; Abur et al., 2018). Speech production involves a dynamic balance between feedback and feedforward control (Civier et al., 2010), and impairment in one type of control leads to a shift of the balance toward the other. Accordingly, individuals with PD may have to increase their reliance on auditory feedback as a consequence of feedforward control impairment during speech production (Chen et al., 2013; Huang et al., 2016), resulting in abnormally enhanced vocal compensations for pitch perturbations (Liu et al., 2012; Chen et al., 2013; Mollaei et al., 2016; Huang et al., 2019) paralleled by hyperactivity in the sensory and motor regions (Huang et al., 2016). In light of this point, c-TBS over the left SMA in individuals with PD may lead to a partial functional restoration of SMA that increases reliance on feedforward control and/or decreases reliance on feedback control, which in turn results in reduced and normalized vocal compensations for pitch perturbations.

Consistently, the observed changes in the cortical P1-N1-P2 responses reflect the neural impact of c-TBS over the left SMA on vocal pitch regulation in individuals with PD. It has been suggested the P1 component is responsible for the earlier detection of deviant auditory feedback in an all-or-nothing manner (Scheerer et al., 2013), while the P2 component reflects the later cortical processing of auditory-motor integration (Liu et al., 2020). Specifically, individuals with PD following c-TBS over the left SMA exhibited decreased P2 responses that were significantly correlated with decreased vocal compensations and source-localized in the right IFG, MFG, PrCG, PoCG, and insula, which is in line with other studies showing the multiple neural generators of the P2 responses in the fronto-temporo-parietal regions (Huang et al., 2016; Guo et al., 2017; Liu et al., 2020). This finding is consistent with the DIVA model that proposes a right-lateralized feedback control of speech production (Golfinopoulos et al., 2011; Tourville and Guenther, 2011). A number of empirical findings have also shown significant contributions of these right-sided regions to auditory feedback control of vocal/speech production (Toyomura et al., 2007; Tourville et al., 2008; Behroozmand et al., 2015; Kort et al., 2016; Guo et al., 2017). Moreover, the high-gamma activity of the right IFG has been shown to be significantly correlated with vocal compensations for pitch perturbations (Kort et al., 2016). Clinically, this right-sided activity pattern was also observed in individuals with PD following voice treatment with LSVT® LOUD, showing increased activity in the right DLPFC, basal ganglia, and insula (Liotti et al., 2003), and a significant correlation between improved vocal loudness and increased activity in the right IFG and MFG (Narayana et al., 2010). More importantly, no significant differences were found in the P1 and P2 amplitudes between individuals with PD following active SMA c-TBS and healthy controls. Therefore, reduced and normalized P1 and P2 responses elicited by c-TBS over the left SMA in individuals with PD may reflect a functional reorganization of speech motor networks that resulted in

decreased reliance on auditory feedback or increased reliance on feedforward control to facilitate the online monitoring of vocal production.

In contrast, the N1 response was enhanced following c-TBS over the left SMA in individuals with PD as compared to sham stimulation and healthy controls. This component reflects higher-level cortical encoding of auditory pitch or phonemic quality in the primary and secondary auditory cortices (Chait et al., 2004) and is sensitive to the size, direction, and timing of vocal pitch perturbations (Behroozmand et al., 2009; Liu et al., 2011). The enhancement of N1 may be indicative of downstream effects of c-TBS over the left SMA. For example, a recent study of 10 sessions of low-frequency rTMS over the right STG in individuals with PD showed increased activation of the SM1 and caudate nucleus during sentence reading (Brabenec et al., 2021). There is evidence for dysfunctional self-monitoring of auditory feedback in PD (Arnold et al., 2014; Railo et al., 2020). For example, N1 responses to self-produced speech were found to be less suppressed in individuals with PD compared to healthy individuals, and responses to passively heard phonemes were observed to be smaller (Railo et al., 2020). This abnormal neural response may exaggerate the mismatch between the intended and actual vocal output (i.e., larger prediction errors) and lead to larger vocal responses. Accordingly, enhancement of the N1 responses following c-TBS over the left SMA may represent a compensatory mechanism that allows individuals with PD to predict the sensory consequence of self-produced speech more precisely (i.e., smaller prediction errors), generating more feedforward commands to correct for pitch perturbations with smaller compensation magnitudes.

Several inherent limitations of the present study should be addressed. First of all, the present study reported the immediate effects of SMA c-TBS on auditory-motor integration for vocal pitch regulation in a single-session manner, limiting the assessment of treatment outcome with the measures of speech characteristics, such as vocal acoustics (e.g., f_0, intensity), articulatory function, and speech intelligibility, and clinical assessment, such as voice handicap index (VHI) and visual analog scale (VAS). Also, the sample size is relatively small, although it is consistent with other studies that investigated PD-related speech disorders (Huang et al., 2016; Mollaei et al., 2016; Brabenec et al., 2019, 2021). In order to fully address the clinical efficacy and long-term effects of c-TBS for the treatment of PD dysarthria, future randomized, double-blind, sham-controlled studies are warranted in a multiple-session manner, and a comprehensive assessment of speech motor skills with larger sample sizes should be conducted in future. Second, responses to the FAF-based vocal production task were not measured for individuals with PD prior to active or sham SMA c-TBS. Asking our individuals with PD to perform the vocal production task twice (before and after c-TBS) would require them to generate a total of 200 consecutive vocalizations. Our pilot tests showed that individuals with PD experienced serious vocal fatigue and other uncomfortable issues that significantly worsened the quality of the vocal and EEG data when producing so many vocalizations. Thus, there may exist baseline variability in the vocal and EEG data between two different days (active and sham SMA c-TBS) that cannot be ruled out in the present study. In addition, passively listening to self-produced voice was not included, making it difficult to determine whether the c-TBS effects observed in individuals with PD are the result of their dysfunctions in auditory processing alone or their dysfunctions in auditory-motor integration. Further work is needed to address this question by examining the modulation of SIS by applying TMS over certain cortical regions.

In summary, the present study showed that c-TBS over the left SMA in individuals with PD led to reduced vocal compensations for pitch perturbations paralleled by reduced P1 and P2 responses and enhanced N1 responses. These findings provide the first neurobehavioral evidence for causal modulations of auditory-motor integration for vocal pitch regulation in individuals with PD by c-TBS over the left SMA, suggesting that neuronavigated c-TBS over speech motor regions may be a promising strategy to facilitate auditory-motor control of vocal production in PD.

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 human participants were reviewed and approved by Institutional Review Board of The First Affiliated Hospital of Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GD, EW, PL, XC, and HL contributed to the design of the study. GD, MW, YL, ZG, TL, YC, and LC contributed to the acquisition and analysis of data. GD, JJ, TL, PL, XC, and HL contributed to drafting the manuscript and preparing the figures. All authors have reviewed and approved the contents of the manuscript.

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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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Aging effects on neural processing of rhythm and meter

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When listening to musical rhythm, humans can perceive and move to beat-like metrical pulses. Recently, it has been hypothesized that meter perception is related to brain activity responding to the acoustic fluctuation of the rhythmic input, with selective enhancement of the brain response elicited at meter-related frequencies. In the current study, electroencephalography (EEG) was recorded while younger (<35) and older (>60) adults listened to rhythmic patterns presented at two different tempi while intermittently performing a tapping task. Despite significant hearing loss compared to younger adults, older adults showed preserved brain activity to the rhythms. However, age effects were observed in the distribution of amplitude across frequencies. Specifically, in contrast with younger adults, older adults showed relatively larger amplitude at the frequency corresponding to the rate of individual events making up the rhythms as compared to lower meter-related frequencies. This difference is compatible with larger N1-P2 potentials as generally observed in older adults in response to acoustic onsets, irrespective of meter perception. These larger low-level responses to sounds have been linked to processes by which age-related hearing loss would be compensated by cortical sensory mechanisms. Importantly, this low-level effect would be associated here with relatively reduced neural activity at lower frequencies corresponding to higher-level metrical grouping of the acoustic events, as compared to younger adults.

KEYWORDS

aging, frequency tagging, EEG, rhythm perception, beat and meter perception

Introduction

When listening to music, listeners entrain to regularities that are perceived as a musical beat, an integral part of music perception (Huron, 2006). These regularities are usually organized into a meter. A metrical structure consists of a pattern of nested pulse-like beats, which can be but are not necessarily, prominent in the acoustic signal itself (Large, 2008). Increasing evidence suggests that meter perception may be related to selective enhancement of neural activity at the meter periodicities and their harmonics, or meter-related frequencies. This selective enhancement can be observed in

the electroencephalography (EEG) signal recorded while listeners are presented with a rhythmic pattern, a series of variable length tones and silences, inducing the perception of a metrical structure (Lenc et al., 2018, 2020, 2021; Nozaradan et al., 2011, 2012, 2016). This selective enhancement has been observed not only in response to regular rhythms with high acoustic energy at the meter frequencies but also in syncopated rhythms, with no prominent acoustic cues to the meter frequencies. These observations suggest that this enhanced neural activity at the meter-related frequencies is not simply stimulus-driven or driven by low-level subcortical processes of the auditory system (Nozaradan et al., 2018a; see also Nozaradan et al., 2016; Lenc et al., 2018, 2020, 2021).

Little is known about the neural processing of rhythmic inputs in older adults. What is known has been focused on speech perception, where overall, the literature suggests that older adults, typically 60+ years, respond more strongly but less precisely to temporally regular stimulation at low (speech-paced) frequencies, approximately 3–4 Hz (Anderson et al., 2012; Bidelman et al., 2014; Goossens et al., 2016; Herrmann et al., 2016; Presacco et al., 2016; Henry et al., 2017), a pattern ascribed to the inhibition theory of aging (Salthouse and Meinz, 1995; Caspary et al., 2008). This theory ascribes an increase in overall brain activity to a decrease in GABA (gamma-aminobutyric acid), an inhibitory neurotransmitter, in the aging brain (Caspary et al., 2008). This decrease in inhibitory activity can also explain the decrease in temporal encoding precision often observed in older compared to younger adults (Anderson et al., 2012; Presacco et al., 2016).

On the other hand, the few pieces of evidence about music perception in older adults suggest that it is generally preserved (Halpern et al., 1995, 1998; Halpern et al., 1996, 2017). In some cases, the performance of a musical task is preserved, but the underlying brain activity changes, suggesting that older adults may automatically compensate for declining cognitive or perceptual abilities in the musical domain (Halpern et al., 2017; Lagrois et al., 2018). This may be due to the development of compensatory mechanisms similar to those found for speech in noise perception, where older adults use contextual information to help overcome age-related changes in hearing and cognitive abilities (Horn and Cattell, 1967; Horn, 1982; Madden, 1992; Birren and Fisher, 1995; Pichora-Fuller et al., 1995). For example, when rating the fit of a note in a melody, older adults relied more heavily on scale degree information, derived from knowledge of the tonal hierarchy, whereas younger adults relied more heavily on note-to-note information (Bharucha and Krumhansl, 1983; Halpern et al., 2017). In addition to increased use of contextual and crystallized knowledge, the neural compensation theory of aging stems from the observation of patterns of over- and under-activation, reduced asymmetry and reduced connectivity of brain activity in the brains of older adults as compared to younger adults when performing a similar task at a similar level (Reuter-Lorenz et al., 2000; Cabeza, 2002; Reuter-Lorenz, 2002; Grady et al., 2003; Cabeza et al., 2004; Reuter-Lorenz and Cappell, 2008; Davis et al., 2011). For example, a frontal shift in activity has been observed in older adults associated with compensation for declining perceptual abilities (Park and Reuter-Lorenz, 2009).

In terms of rhythm perception, Sauvé et al. (2019) used frequency tagging to compare neural activity in older and younger adults while passively listening to a metronome. This study found that older adults, compared to younger adults, had reduced amplitude of neural activity at the frequency of the metronome and to a lesser extent also at the first three harmonics of the metronome frequency (Sauvé et al., 2019), which could not be fully accounted for by age-related changes in hearing as measured by pure-tone thresholds. In other words, older adults demonstrated a reduced response to the metronome frequency compared to younger adults, a pattern in line with literature suggesting that temporal precision degrades in the aging brain (Anderson et al., 2012; Herrmann et al., 2019).

The goal of the current study was to explore differences in neural processing of rhythm between older adults and younger adults actively listening to two rhythms. One rhythm contained prominent acoustic energy at the meter-related frequencies compared to meter-unrelated frequencies (i.e., non-syncopated rhythm). In contrast, the second rhythm was characterized by a lack of prominent acoustic energy at meter-related frequencies compared to meter-unrelated frequencies (i.e., syncopated rhythm; see Lenc et al., 2018, 2020). In the syncopated rhythm, perception of the meter thus likely relies on endogenous processes, and selective enhancement of the neural activity at meter-related frequencies cannot be explained by acoustic confound or subcortical processing enhancing prominent acoustic features of the input (Lenc et al., 2020). To the best of our knowledge, the current study is thus the first to explore the impact of aging on neural processing of rhythm, especially when the meter is inferred but not conveyed by a strictly (i.e., metronomic) or strongly periodic (i.e., non-syncopated) stimulus.

Based on our previous findings (Sauvé et al., 2019), together with the fact that older adults have increased exposure to musical patterns due to their age, and that older adults rely on internalized musical structure as a way to compensate for age-related hearing impairment as compared to younger adults (Halpern et al., 2017), it is expected that older adults will show similar neural activity to younger adults in response to both rhythms despite age-related hearing loss, thus with preserved selective enhancement at the meter-related frequencies irrespective of rhythm complexity. Furthermore, one of the hallmarks of aging is that older adults tend to have more difficulty processing stimuli presented at a faster rate (Salthouse and Meinz, 1995). It is therefore possible that differences between older and younger adults are more pronounced at a higher tempo. Finally, given known topographic neural shifts associated with aging (e.g.,

TABLE 1 Participant demographics.

	Age	Formal education (years)[a]	Pure-tone average (dB HL)[b]
Younger adults	20.3 (1.84)	14.6 (2.23)	6.2 (5.07)
Older adults	63.4 (3.68)	12.87 (3.46)	13.28 (9.03)

[a] $t(28) = 1.6$, $p \geq 0.05$; standard deviation in brackets.
[b] Binaural average of pure-tone threshold at 500, 1,000, and 2000; $t(28) = 40.55$, $p < 0.05$; standard deviation in brackets.

Park and Reuter-Lorenz, 2009), we also examined possible differences in topographic maps between older and younger adults. We expected to find selective enhancement at meter-related frequencies over a larger surface for older adults than for younger adults.

Materials and methods

Participants

Twenty-nine participants (the same as in Sauvé et al., 2019) took part in this study and provided written informed consent in accordance with the Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland. Participants were divided into two *age groups*: 15 older adults (>60 years; 10 female) and 14 younger adults (<25 years; 7 female). All participants self-reported being healthy, right-handed and free of any cognitive deficit. All participants were non-musicians, although some had music training in childhood (specifically, 8 younger and 2 older adults). Hearing abilities were assessed using standard clinical pure-tone (PT) audiometry, which revealed significant differences between the two age groups, as detailed in **Table 1**. There was no difference in hearing thresholds between participant who had received some musical training and those who had received none [$t(28) = -1.84$, $p > 0.05$]. All participants received a small cash honorarium for their participation. **Table 1** summarizes participant demographics.

Stimuli

The selected rhythmic patterns were similar to those of previous studies (Nozaradan et al., 2016, 2017, 2018b; see also Lenc et al., 2018) and presented into four *conditions*: two *rhythms* (*non-syncopated* and *syncopated*) at two *tempi* (*slow*: 0.416 Hz cycle rate, i.e., rhythmic pattern of 2,400 ms duration; and *fast*: 0.833 Hz cycle rate, i.e., 1,200 ms pattern duration). The structure of the rhythms was based on the alternation of 12 events, consisting of sounds and silent intervals (**Figure 1**). The individual sounds consisted of 1,000 Hz pure tones, presented at ∼75 dB SPL, with 10 ms rise and fall times, and were either 100 or 200 ms long for the fast or slow tempo, respectively. All stimuli were presented via insert earphones (Etymotic E3A). As described in Nozaradan et al. (2016) and Lenc et al. (2018), rhythms were designed to induce the perception of a meter based on a preference for grouping by 2 and 4 events per cycle (grouping by 4 events corresponding to the periodicity mostly tapped by participants when asked to tap on the rhythm; see Lenc et al., 2018). The first rhythm could be considered non-syncopated, as the rate of the perceived meter levels closely matched with the groups of acoustic events making up the rhythm. This matching was corroborated by frequency-domain analysis of the envelope of acoustic signal, confirming prominent acoustic energy at the meter-related frequencies (see also Lenc et al., 2021 for complementary measures of syncopation on the same rhythm). In contrast with the first rhythm, the second rhythm was considered syncopated, as the rate of the perceived meter levels did not closely aligned with the groups of sounds making up the rhythm, due to a more irregular arrangement of groups of tones and silent intervals making up the rhythm. This was also reflected in frequency-domain analysis of the envelope of the acoustic stimulus, showing that the meter-related frequencies were not salient in the stimulus (Lenc et al., 2021). Stimuli were generated in Reaper (V 5.16) and presented to participants using Eprime (V 3.0).

Procedure

After providing written informed consent, participants completed a short demographics questionnaire and were given the possibility to practice tapping to the 4 rhythms that would be presented during the study. Each participant was prepared for EEG recording and was seated in a double-walled, electrically shielded sound-attenuating booth (Eckel). Participants were given a response box (Chronos, EPrime) and could see a computer monitor. They were further instructed to tap their index finger with their dominant hand in time with the perceived beat while listening to the stimuli. They tapped on one of the response buttons whenever the green light came up on the response box, and the computer monitor said, "Tap." When the response box buttons became red and the computer monitor said "Stop Tapping," participants were instructed to stop tapping but to maintain the beat mentally while the stimuli continued playing. Each participant was told that they would be expected to start tapping as soon as the green light came back on. Alternating between a Tapping Phase and a Listening Phase was done to ensure that participants actively maintained the meter throughout the task. To avoid eye movement, participants were told to either fixate on the monitor or response box during the task and to minimize switching between the two.

The two rhythms (non-syncopated, syncopated) were presented at the two tempi (slow, fast) in four separate blocks.

The order of the blocks was identical for each participant (non-syncopated rhythm, slow and fast, and then syncopated rhythm, slow and fast). This fixed order was used to ensure that participants could easily tap the perceived meter during the tapping phase and were thus likely to perceive the meter also when listening without tapping. Indeed, pilot testing suggested that participants had increased difficulty tapping to the fast vs. slow stimuli, and to the syncopated vs. the non-syncopated rhythm, even after a short practice session. In contrast, the participants seemed overall more comfortable tapping when they were first presented with the non-syncopated rhythms and the slow tempi. Each block started with a Tapping Phase that lasted 48 s. After this Tapping Phase, there were 10 repetitions of a 48 s Listening Phase and a 12 s Tapping Phase.

Electroencephalography data processing

Neuroelectric brain activity was digitized at a sampling rate of 1024 Hz from 134 electrodes using the radial layout system, with a highpass filter set at 0.1 Hz using a Biosemi ActiveTwo system (Biosemi Inc., Amsterdam, Netherlands). Six electrodes were placed bilaterally at mastoid, inferior ocular and lateral ocular sites.

Data wereanalysed using the Letswave 6[1] (Mouraux and Iannetti, 2008) signal processing toolbox for Matlab. Eye blinks and eye movements were identified for each participant using an independent component analysis (ICA). Components related to eye movements were removed from the EEG signal. Next, the EEG data were referenced to the average of all scalp electrodes. Each condition was divided into ten 48 s epochs corresponding to the Listening Phases and then averaged into a single 48 s epoch, yielding four epochs (*non-syncopated slow*, *syncopated slow, non-syncopated fast, syncopated fast*) per channel and participant. EEG data recording during the tapping phase was not used for further analysis, as the purpose of the current study was not to focus on the neural activity related to overt rhythmic movement production. However, this limited tapping data can provide a behavioral index about the perceived meter using inter-tap interval (ITI) information (see **Supplementary material**).

To measure the amplitude at the meter-related and meter-unrelated frequencies elicited in response to the rhythms, a fast Fourier transform (FFT) was applied to the four EEG epochs for each EEG channel and participant, with a resulting spectral resolution of approximately 0.02 Hz (i.e., 1/48 s). These spectra were then corrected using a noise subtraction with bin range (±) 3–13 (0.2 Hz on each side beginning at 0.06 Hz). This function, which subtracts from the amplitude at each frequency bin the amplitude averaged across the neighboring frequency bins from the 3rd to the 13th bin on each side (Mouraux et al., 2011; Nozaradan, 2013; Nozaradan et al., 2015), thus centers the amplitude spectrum around zero. Therefore, the amplitude measured at the target frequencies should tend toward zero if no significant neural activity is elicited at those specific frequencies. The amplitude of neural activity obtained from this analysis will be referred to as simply *amplitude* throughout this paper.

For each *condition,* the amplitudes at targeted frequency bins were extracted from a montage of frontocentral electrodes in increasingly large concentric circles (see **Figure 2**). The *core circle montage* was selected based on signal distribution and consistent with previous work (Nozaradan et al., 2012, 2016; Lenc et al., 2018), while each subsequent *outer circle* includes one electrode in each direction from the core. This analysis was done to investigate any potential topographical differences between age groups. Previous work has suggested a compensation theory of aging (Reuter-Lorenz and Cappell, 2008), which predicts larger responses or more widespread activation in older adults. Given that the magnitude of the response and the extent of the spatial distribution are difficult to separate, it is important to test both possible effects by comparing both the magnitude of the responses and their spatial spread. By testing topographic patterns as a function of age, the possibility of age-related differences during meter perception tasks can be explored.

As in Lenc et al. (2018), the amplitude at 12 target frequencies was extracted, corresponding to the duration of the whole pattern/cycle rate (0.416 or 0.833 Hz for the two different tempi, respectively) and its harmonics up to the period of single acoustic events (5; 10 Hz). These 12 frequencies were then tagged as meter-related frequencies and meter-unrelated frequencies (Lenc et al., 2018). The meter-related frequencies were based on the periodicities of the meter assumed to be perceived for these rhythms and their harmonics, as informed by behavioral data collected in a large number of participants in previous studies (Nozaradan et al., 2016, 2018b; Lenc et al., 2018) and corroborated by the tapping data collected during the Tapping Phases. These meter periodicities consisted in the smallest inter-sound intervals (100 and 200 ms for the fast and slow tempi respectively), and grouping of these intervals by 2, 4, and 12 intervals (see Lenc et al., 2018, for example), thus yielding four meter-related frequencies (i.e., the 1st, 3rd, 6th, and 12th frequencies from the 12 target frequencies, further labeled F1, F3, F6, and F12). The remaining frequencies were considered meter-unrelated. Amplitudes were obtained for each frequency of interest from the closest spectral bin from each frequency.

Statistical analysis

Statistical analyses were conducted using mixed effects multiple linear regression modeling implemented in the R (3.3.2) *lme4* (Bates et al., 2015) package. All analysis models

1 https://www.letswave.org/

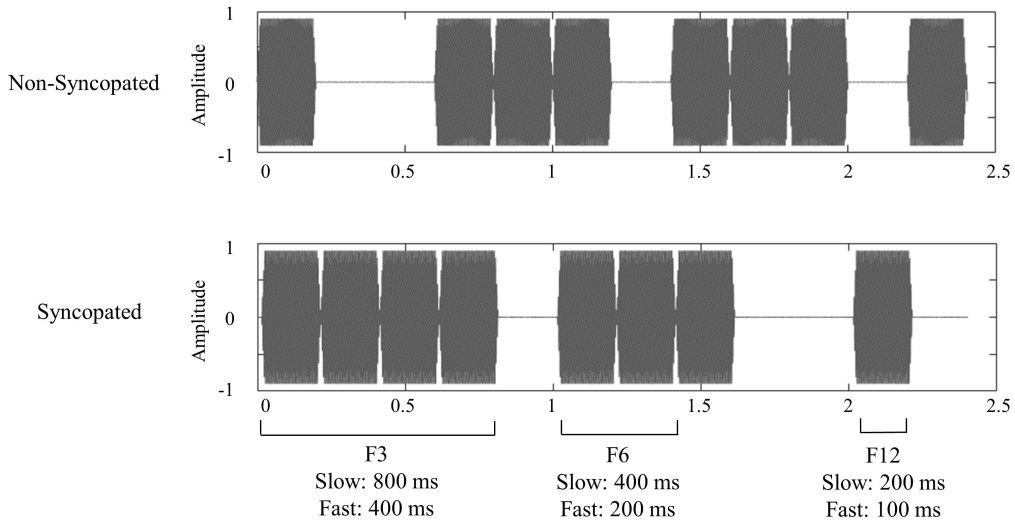

FIGURE 1
Audio signal representation of the non-syncopated and syncopated rhythms at slow tempo (with 200 ms individual sounds).

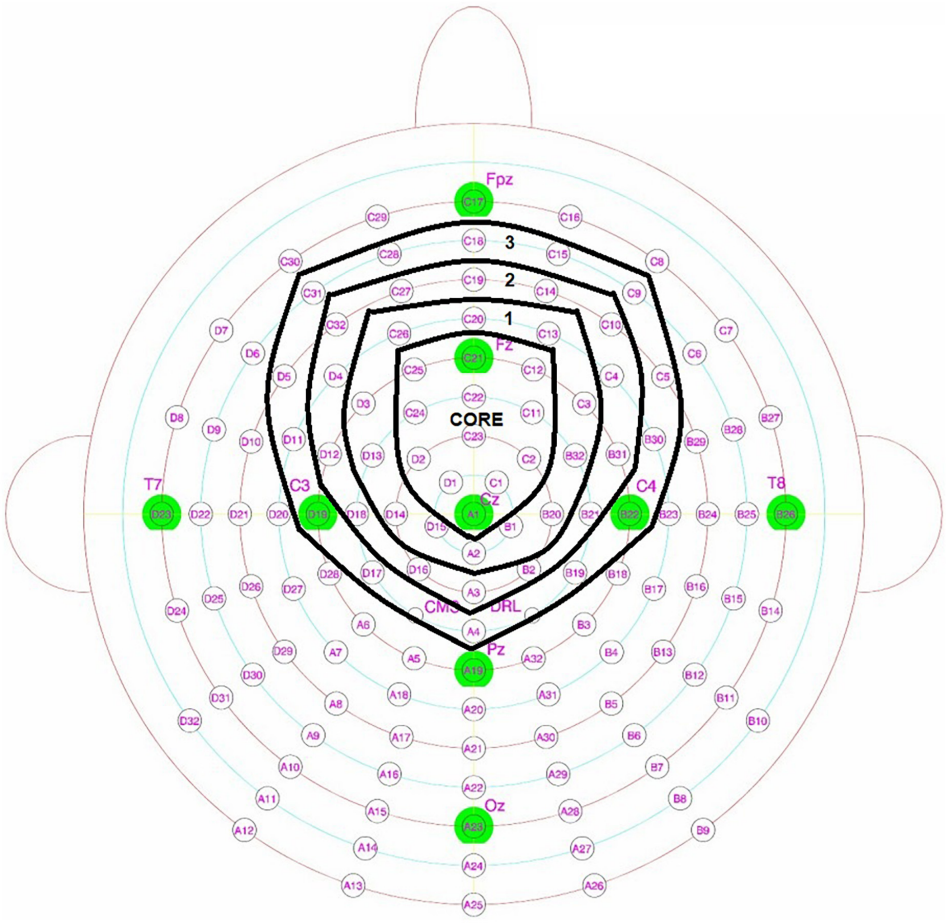

FIGURE 2
128 + 2 radial electrode layout illustrating core and outer circle electrode montages.

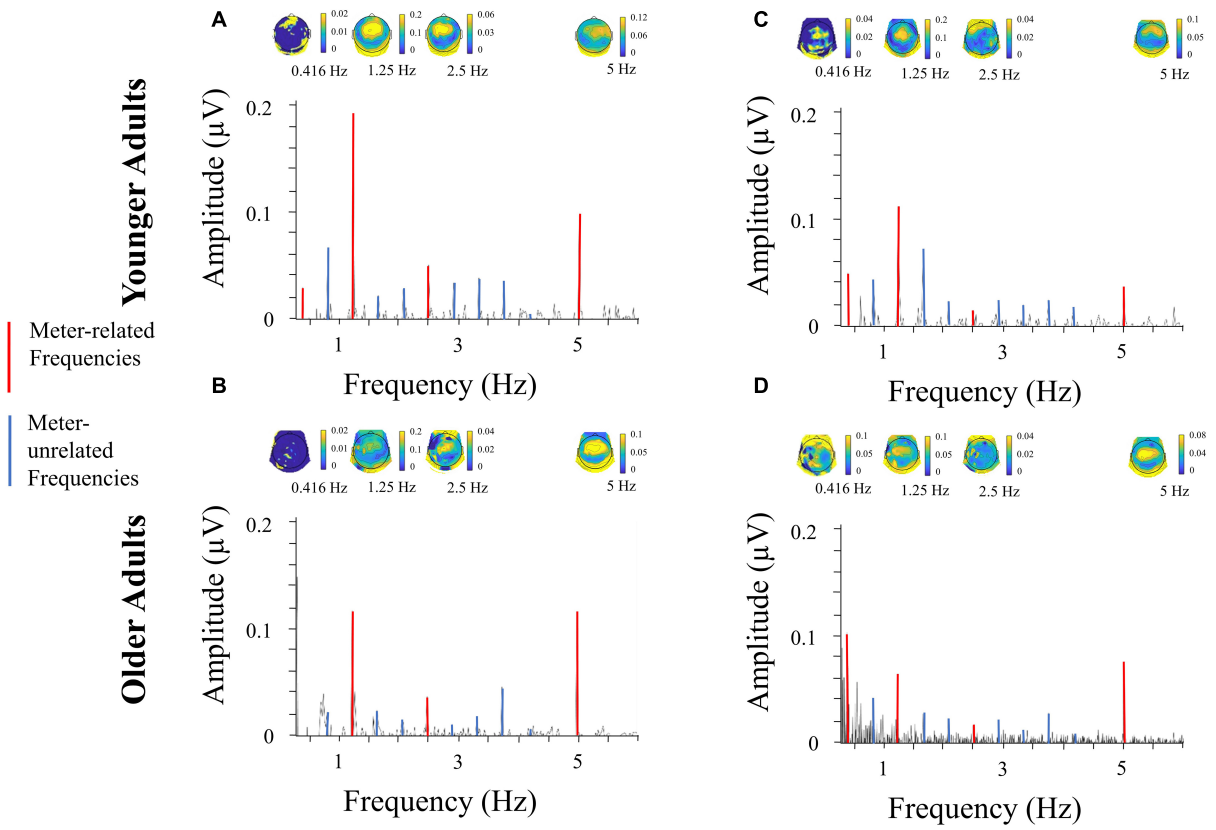

FIGURE 3
EEG spectra, slow tempo. Amplitude of neural activity at electrode Cz ranging from 0.5 to 6 Hz for *younger adults* **(A,C)** and *older adults* **(B,D)** adults for *non-syncopated* **(A,B)** and *syncopated* **(C,D)** rhythms for *slow tempo*, along with topographic maps corresponding to each meter-related frequency. Frequency and amplitude scales are identical across conditions and groups to allow direct comparison across spectra. The scales of the topographical maps are adjusted for each condition, group and frequency for optimal visualization of topographical distribution across the EEG channels. Each topographical map corresponds to a meter-related frequency, shown in red.

were maximally fitted to reflect the experimental design, as per Barr et al. (2013), where models included random intercepts on participants and random slopes on participants by stimulus condition. All categorical variables were factors, where each level was compared to a base level. These base levels are *slow* for *tempo*, *non-syncopated* for *rhythm*, *younger* for *age group*, *meter-related* for *frequency type, F3* for *frequency, no training* for *musicianship* and *core* for *electrode montage*. Note that the choice of base level does not affect the overall results of the model, only the direction and magnitude of the coefficients. For example, mean frequency amplitudes remain constant; reporting differences between each frequency and F3 would result in different numbers than reporting differences between each frequency and F6. Models were evaluated using Pearson's correlation between the model's predictions and the data along with the correlation's 95% CIs. Statistical significance of each individual factor level for a given predictor was evaluated using 95% CIs, where an interval not including zero indicates a significant predictor. In each analysis, follow-up independent sample two-tailed *t*-tests with Bonferroni correction were conducted to investigate simple effects of age. Alpha was 0.05.

Frequency analysis

For each participant and condition, we first averaged the amplitudes for meter-related frequencies and meter-unrelated frequencies separately. Then, we compared the amplitude of the response at meter-related and meter-unrelated frequencies to measure selective enhancement of brain activity at meter-related frequencies across stimuli. This is especially important in the case of the syncopated rhythm, which does not include prominent meter-related frequencies. To do so, a linear mixed effects model predicting spectral amplitude of neural activity included *frequency type* (*meter-related, meter-unrelated*), *tempo* (*slow*, *fast*), *rhythm* (*non-syncopated, syncopated*), *musicianship* (*no training, training*), and *age group* (*younger, older*) as fixed effects including interactions and *PTAv* (pure tone threshold

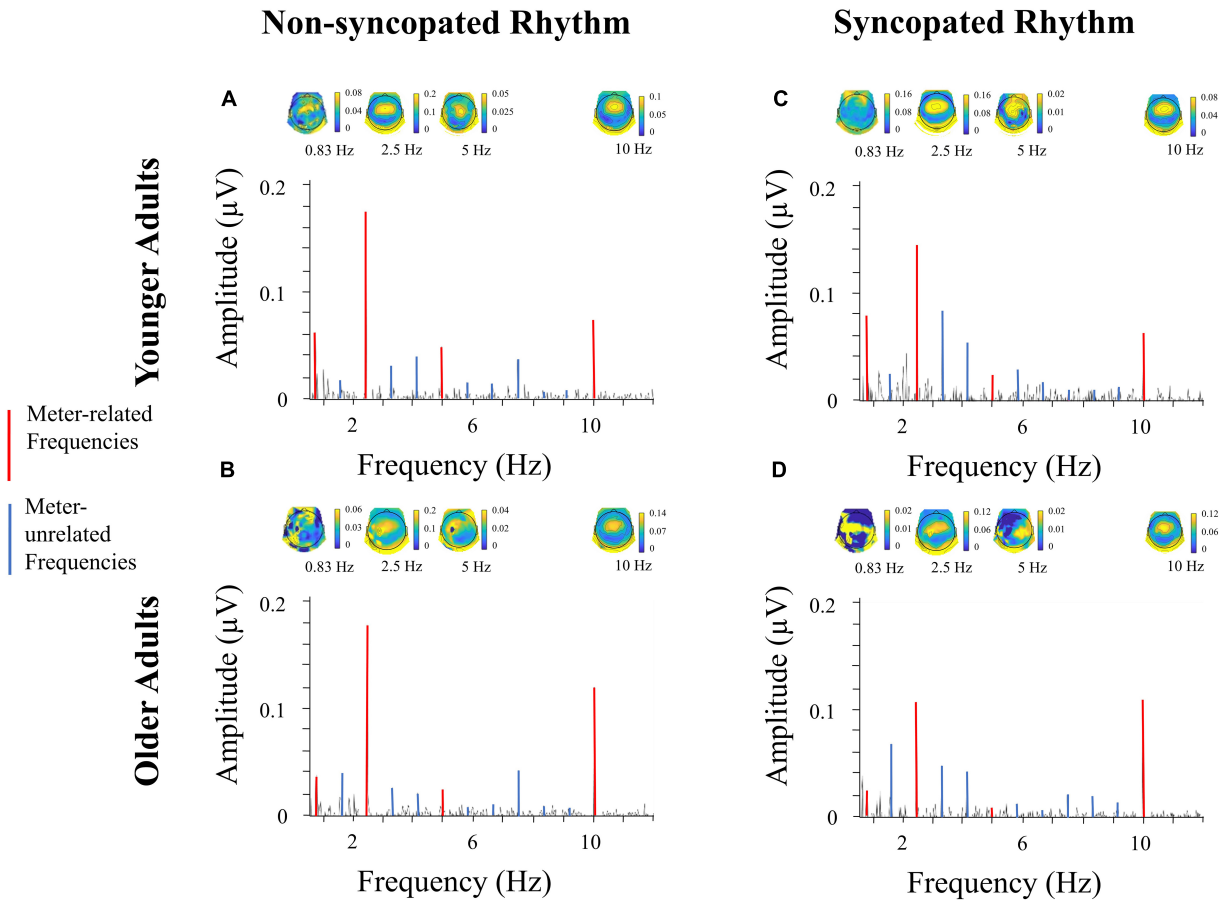

FIGURE 4
Electroencephalography (EEG) spectra, fast tempo. Amplitude of neural activity at electrode Cz ranging from 0.9Hz to 12Hz for *younger adults* **(A,C)** and *older adults* **(B,D)** for *non-syncopated* **(A,B)** and *syncopated* **(C,D)** rhythms for *fast tempo*, along with topographic maps corresponding to each meter frequency. Frequency and amplitude scales are identical across conditions and groups to allow direct comparison across spectra. The scales of the topographical maps are adjusted for each condition, group and frequency for optimal visualization of topographical distribution across the EEG channels. Each topographical map corresponds to a meter-related frequency, shown in red.

average) score as a fixed main effect. PTAv was calculated by taking the binaural average of pure-tone threshold at 500, 1,000, and 2,000 Hz and was used to check for low-level effects of poorer hearing in older adults while channel accounts for variance between electrodes. As expected, the PTAv was larger in older adults compared to younger adults, demonstrating normative age-related changes in hearing thresholds (see Table 1).

Next, to investigate age effects on meter-related entrainment, a model predicting spectral amplitude of neural activity in response to meter-related frequencies included *tempo* (*slow, fast*), *rhythm* (*non-syncopated, syncopated*), *frequencies* (*F1, F3, F6, F12*), *age group* (*younger, older*), and *PTAv* score as fixed effects. In all models, interactions with PTAv were not modeled. Finally, the neural compensation hypothesis predicts more widespread activation in older adults than in younger adults (Reuter-Lorenz and Cappell, 2008). To test this, *montage (core, outer 1, outer 2, outer 3)* was added to the meter-related entrainment model as a fixed effect, including interactions (except with PTAv).

Tapping analysis

The tapping task was included to ensure the participant was focusing on the metrical structure while further listening without moving. The tapping data were also used as a behavioral index confirming the assumed perceived metrical structure. As expected, participants were mostly tapping at intervals aligning with grouping by two, four, or eight intervals, with the majority converging on groupings of 4 (see **Supplementary material 2**). Mean (standard deviation) ITIs for slow non-syncopated, fast non-syncopated, slow syncopated and fast syncopated conditions were 781.1 (186.1), 400.34 (97.2), 791.4 (193.2), and 434.1 (135.7), respectively, where 800 and 400 ms represent groupings of 4 for the slow and fast conditions, respectively. Because only a small number of taps were recorded between

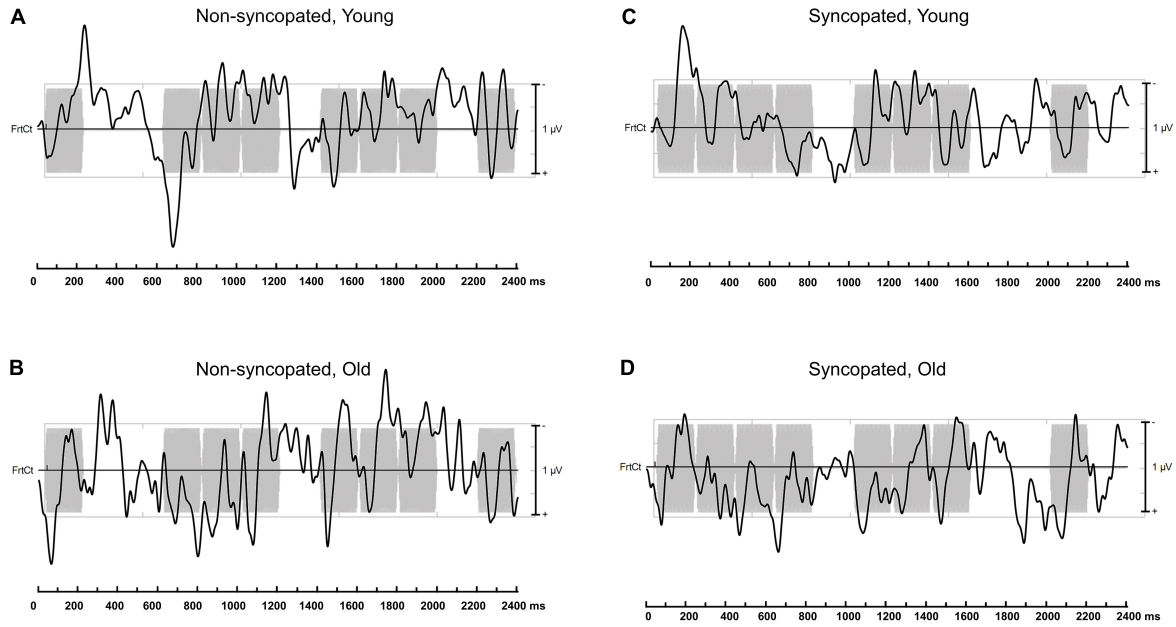

FIGURE 5
Electroencephalography (EEG) data presented in the time-frequency domain averaged across each repetition of the rhythm and the montage of fronto-central electrodes used in analysis for *younger adults* **(A,C)** and *older adults* **(B,D)** for *non-syncopated* **(A,B)** and *syncopated* **(C,D)** rhythms for *slow tempo* overlaid onto their respective auditory stimuli.

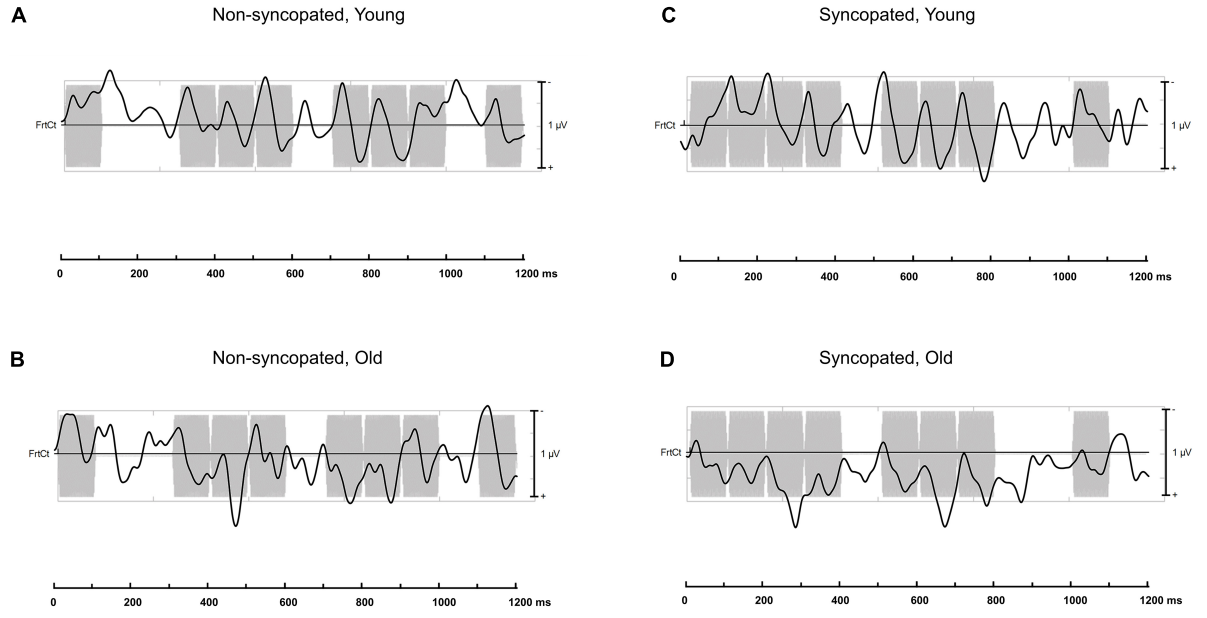

FIGURE 6
Electroencephalography (EEG) data presented in the time-frequency domain averaged across each repetition of the rhythm and the montage of fronto-central electrodes used in analysis for *younger adults* **(A,C)** and *older adults* **(B,D)** for *non-syncopated* **(A,B)** and *syncopated* **(C,D)** rhythms for *fast tempo* overlaid onto their respective auditory stimuli.

each rest period and because a proper analysis of the precision of tapping, for example, requires a significantly higher number of taps (i.e., >100 in Zendel et al., 2011), the tapping data were not used for further exploration of the tapping performance. Instead, the data are presented with a cursory analysis of mean inter-tap interval as **Supplementary material 2**.

TABLE 2 Summary of significant simple musicianship effects for frequency type analysis, including tempo, rhythm, frequency type, and age.

Tempo	Rhythm	Frequency type	Age	Statistic	Degrees of freedom	Effect size
Slow	Non-syncopated	Meter-related	Younger	−3.30	655	−0.25
		Meter-unrelated	Younger	−3.42	1,260	−0.18
	Syncopated	Meter-related	Younger	−9.69	644	−0.70
		Meter−unrelated	Younger	−4.18	1,301	−0.23
			Older	6.20	371	0.34
Fast	Non-syncopated	Meter-unrelated	Older	4.85	285	0.32
	Syncopated	Meter-related	Younger	−6.38	571	−0.48

The *t*-statistic along with degrees of freedom and Cohen's *d* are reported.

Results

Meter-related vs. meter-unrelated frequencies

First, we tested for selective enhancement of brain activity elicited at frequencies corresponding to the meter by comparing amplitudes at meter-related frequencies vs. meter-unrelated frequencies using a linear mixed effects model. **Figures 3**, **4** present the brain responses along with topographic maps for each meter-related frequency for the *slow* and *fast* tempi, respectively. **Figures 5**, **6** present the time-domain EEG response overlaid with the acoustic stimulus. The model's predictions were significantly correlated with the data, $r = 0.39$, 95% CIs [0.38,0.40], $p < 0.01$; full model details can be found in **Supplementary material 1**. Main effects of *tempo* (*slow* > *fast*), *rhythm* (*non-syncopated* > *syncopated*), *frequency type* (*meter-related* > *meter-unrelated*), and *musicianship* (*training* > *no training*) were significant while *age group* (*younger* > *older*) and *PTAv* were not. Only *intercept* and *frequency type* had R^2 values over 0.01,0.07, and 0.10, respectively, indicating that the random effects and frequency type had the most explanatory power of all the predictors. Significant interactions include all two-way interactions except for between *rhythm* and *tempo*, *frequency type* and *age*, and *tempo* and *age*, three-way interactions between *age*, *rhythm* and *frequency type*, *age*, *tempo*, and *rhythm*, *musicianship*, *rhythm* and *frequency type*, *musicianship*, *tempo* and *frequency type*, *musicianship*, *age* and *frequency type*, and four-way interactions between *age*, *tempo*, *rhythm* and *frequency type*, and *musicianship*, *age*, *tempo* and *frequency type*. These interactions were driven by the size of the effect of frequency type, musicianship and age.

In the case of frequency type, the effect was similar for the *fast syncopated*, *slow non-syncopated* and *fast syncopated* conditions [$d = 0.57$, t (1865) = 14.66, $p < 0.012$ (Bonferroni corrected), $d = 0.59$, t (1727) = 14.47, $p < 0.012$ and $d = 0.59$, t (2474) = 15.88, $p < 0.012$ respectively], and larger for the *fast non-syncopated* condition [$d = 0.97$, t (1523) = 24.86, $p < 0.012$]. Musicianship had an effect for young adults at the slow tempo for both rhythms and frequency types, as well as in the fast syncopated condition for meter-related frequencies (see **Table 2**). Musicianship had an effect for older adults in the slow syncopated condition for meter-unrelated frequencies and in the fast non-syncopated condition for meter-unrelated frequencies (see **Table 2**). For younger adults, musicianship led to higher amplitudes; for older adults, to lower amplitudes. See **Supplementary material 1** for details of all musicianship follow-up tests. In the case of age, **Figure 7** illustrates the size of the effects. To summarize, in the slow conditions for meter-related frequencies, older adults had higher amplitudes than younger adults. In the slow conditions for meter-unrelated frequencies, older adults had smaller amplitudes than younger adults. Age differences were smallest in the fast conditions. Not all of these age comparisons were significant (see **Figure 7**). There was no main effect of age, but there were some interactions involving age, showing that selective enhancement of meter frequencies was larger in younger adults in some conditions but not all conditions (e.g., meter-related frequencies at slow tempo). A more detailed analysis of meter-related frequencies (section "Amplitude across meter-related frequencies") explores age differences further. **Figure 7** illustrates the mean amplitude of neural activity for all meter-related and meter-unrelated frequencies and all four conditions for older and younger participants.

Amplitude across meter-related frequencies

Next, we analyzed the amplitudes across the meter-related frequencies to determine whether the pattern of distribution of the amplitudes was affected by age (Sauvé et al., 2019). **Table 3** presents the linear mixed effects model for the amplitude of neural activity elicited at meter-related frequencies for all participants across conditions. For brevity, only significant predictors with R^2 above 0.01 were included in **Table 3**; full tables can be found in **Supplementary material 1** along with corresponding summary statistics. Significant predictors included main effects of *rhythm* (*non-syncopated* > *syncopated*),

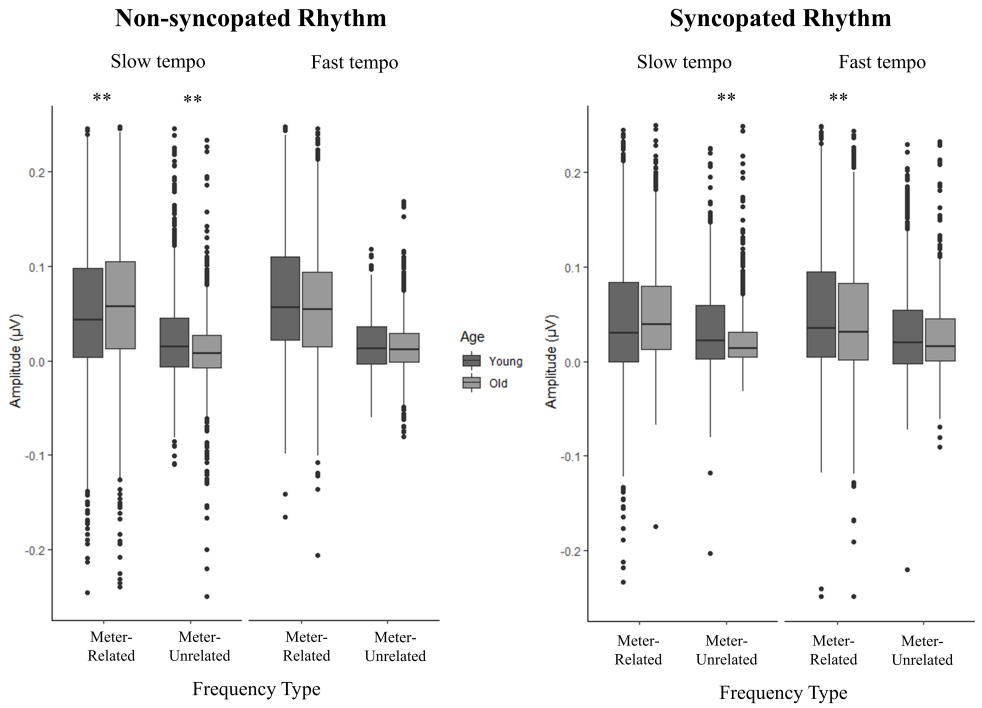

FIGURE 7
Amplitude of neural activity at meter-related and meter-unrelated frequencies across the four conditions and groups. Boxes represent the first quartile, median and third quartile of data, vertical lines the maximum and minimum values as defined by third and first quartile ± 1.5 times the interquartile-range (third quartile - first quartile), with points representing outliers; data represents amplitude values for each frequency (4 m-related and 8 m-unrelated frequencies), channel (12 channels) and participant, totaling approximately 720 and 1440 data points for meter-related and meter-unrelated frequency types, respectively. $^{**}p < 0.006$ (Bonferroni corrected).

age group (*younger* > *older*), and *frequency* (*F1* < *F3* > *F6* < *F12*, *or F1* < *F6* < *F12* < *F3*) as well as multiple two-, three- and four-way interactions. To further understand the interactions of *age group* with *tempo*, *rhythm* and *frequency*, follow-up t-tests were conducted (see **Supplementary material 1**). Age effects were observed at F3 in all but one tempo and rhythm condition (slow syncopated), where younger adults had larger amplitudes than older adults (**Figure 8**, $p < 0.003$). Younger adults also had significantly larger amplitudes than older adults at F6 for the slow non-syncopated and fast syncopated conditions, while age groups had similar amplitudes at F6 for the fast non-syncopated and slow syncopated conditions. An age effect was significant at F1 in all but one condition (slow non-syncopated). At F1, younger adults had larger amplitudes than older adults in the fast non-syncopated and syncopated conditions while older adults had larger amplitudes than younger adults in the slow non-syncopated and syncopated conditions. This opposite age effect, where older adults had larger amplitudes than younger adults, was observed at F12 in all conditions but was not significant in the slow syncopated condition. In summary, younger adults had larger amplitudes than older adults at F1 in the fast tempo condition, and F3 and F6 at both tempi. Older adults had larger amplitudes than younger adults at F1 in the slow tempo condition and at F12 for both tempi. **Figure 8** presents the mean amplitude for younger and older adults as a function of rhythm, tempo, and frequency.

Finally, in order to further characterize the amplitude profiles, *t*-tests with Bonferroni correction were conducted between F3 and F1 and F3 and F12 amplitudes for each age group and condition (see **Figure 8** and **Supplementary material 1** for details). F3 had larger neural amplitude than F1 for both age groups in all conditions except for older adults in the slow syncopated condition ($p < 0.006$). The F3 was larger than the F12 in younger adults, while this difference was not significant in older adults, except during the fast non-syncopated condition.

Neural compensation

Finally, we investigated the distribution of the signal at meter-related frequencies to test the hypothesis that older adults demonstrated more widespread neural activation than younger adults. First, the main effect of *montage* was significant, where overall mean amplitude decreased with increasing distance from the *core montage*. This main effect was qualified by a two-way interaction with *frequency*, and a three-way interactions with *age* and *frequency*, and *tempo* and *frequency*. The three-way interaction involving age is driven by the difference between

TABLE 3 Summary of significant predictors with $R^2 > 0.01$ from the maximally fitted multiple linear regression model predicting neural activity amplitude at meter-related frequencies, including coefficient, Wald 95% confidence intervals and R^2 for each predictor (where there are multiple levels, R^2 is given for the predictor as a whole).

Predictor	Coefficient	2.5%	97.5%	R^2
Intercept	0.22	0.19	0.24	0.10
F1	−0.22	−0.24	−0.20	0.20
F6	−0.15	−0.17	−0.14	
F12	−0.13	−0.15	−0.11	
Age:F1	0.06	0.03	0.08	0.01
Age:F6	0.06	0.03	0.08	
Age:F12	0.12	0.10	0.15	
Rhythm:F1	0.17	0.14	0.19	0.03
Rhythm:F6	0.06	0.04	0.09	
Rhythm:F12	0.10	0.07	0.12	
Tempo:Rhythm:F1	−0.14	−0.18	−0.11	0.01
Tempo:Rhythm:F6	−0.06	−0.10	−0.03	
Tempo:Rhythm:F9	−0.09	−0.12	−0.05	

Random effects account for <0.01 variance and are therefore not reported.
$r = 0.64$, 95% CIs [0.63, 0.66], $p < 0.01$.

F3 and F12, where younger adults have larger amplitudes than older adults at F3 and vice versa for F12. In terms of frequency, the overall pattern was similar across electrode montages except for F1, where the amplitude of F1 diminished faster than the other target frequencies as distance from the core increased. In summary, we did not find any evidence of more widespread neural activation in older adults as compared to younger adults.

Discussion

In this study, we examined differences between older and younger adults in neural activity to a syncopated and a non-syncopated rhythm presented at two different tempi. Overall, the amplitude of neural activity elicited at meter-related frequencies was larger compared to the activity elicited at frequencies unrelated to meter periodicities, even in the syncopated rhythm where the meter-related frequencies are not prominent acoustic features of the input. This finding is consistent with previous work (Nozaradan et al., 2016, 2018b; Lenc et al., 2018, 2020). Most importantly for our experiment, this effect was similar across older and younger adults, thus suggesting that the processes by which the meter-related frequencies are selectively enhanced is generally preserved in aging, in some conditions diminished and in others augmented, despite hearing loss. Moreover, the difference in pure tone audiometric thresholds between age groups did not have a significant impact on the amplitudes of neural activity. Therefore, differences in neural activity observed here between age groups are unlikely to be fully attributable to low-level hearing abilities. It is worth noting that the method used here cannot dissociate whether a difference in z-score values of meter-related frequencies across group is due to differences in the magnitude of neural responses, their timing, or both (Rajendran et al., 2017). However, the fact that the method is sensitive to both differences in amplitude and differences in phase stability at the tagged frequencies over the long trials precisely makes it a highly sensitive measure to capture any difference in selective enhancement of meter-related frequencies. Such a high sensitivity is critical for comparison of EEG responses across groups. Notably, despite this high sensitivity, no significant difference was observed across age groups. This null result suggests that older participants showed fairly preserved neural responses to acoustic rhythms despite significant peripheral hearing loss. Interestingly, the experience of musical training had opposing effects on the age groups. For younger adults, some musical training is related to higher amplitudes; for older adults, to lower amplitudes, though there was rarely a significant difference for older adults. This may be due to the recency, or lack thereof, of said musical training. In other words, childhood musical training for younger adults is more recent than childhood musical training for older adults. Our results suggest that the benefit of musical training disappears after a certain amount of time without training. Future studies collecting more detailed information about musical experience can further investigate this effect.

Though both age groups show selective enhancement at the meter periodicities, the distribution of amplitudes across the different meter-related frequencies differs between age groups. In older adults, we observe lower amplitude at F3 across stimulus conditions compared to younger adults, consistent with an overall decline in delta band frequency activity in normal aging (Polich, 1997). This age effect is in line with the findings of Sauvé et al. (2019), where the same participants were listening to an isochronous rhythm at 1.25 and 2.5 Hz and where older adults had lower amplitudes at the stimulus fundamental frequency (analogous to F3 in this study) than younger adults. In contrast, this effect does not directly fit with the speech neural entrainment literature which shows increased amplitude of neural activity at low (syllable-paced) frequencies of 3–4 Hz in older adults (Goossens et al., 2016; Herrmann et al., 2016, 2019). One case where younger adults showed higher neural amplitude in response to a 2.8 Hz frequency-modulated stimulus than older adults involved attentional control: younger adults demonstrated more activity at 2.8 Hz in an active task when compared to as passive task, where older adults had no difference and had activity similar to younger adults during the passive task (Henry et al., 2017). However, in Sauvé et al. (2019), the task was passive, so attentional control cannot explain younger adults' larger amplitudes as compared to younger adults. Furthermore, these studies only investigated neural responses at the fundamental frequency corresponding to the periodicity of

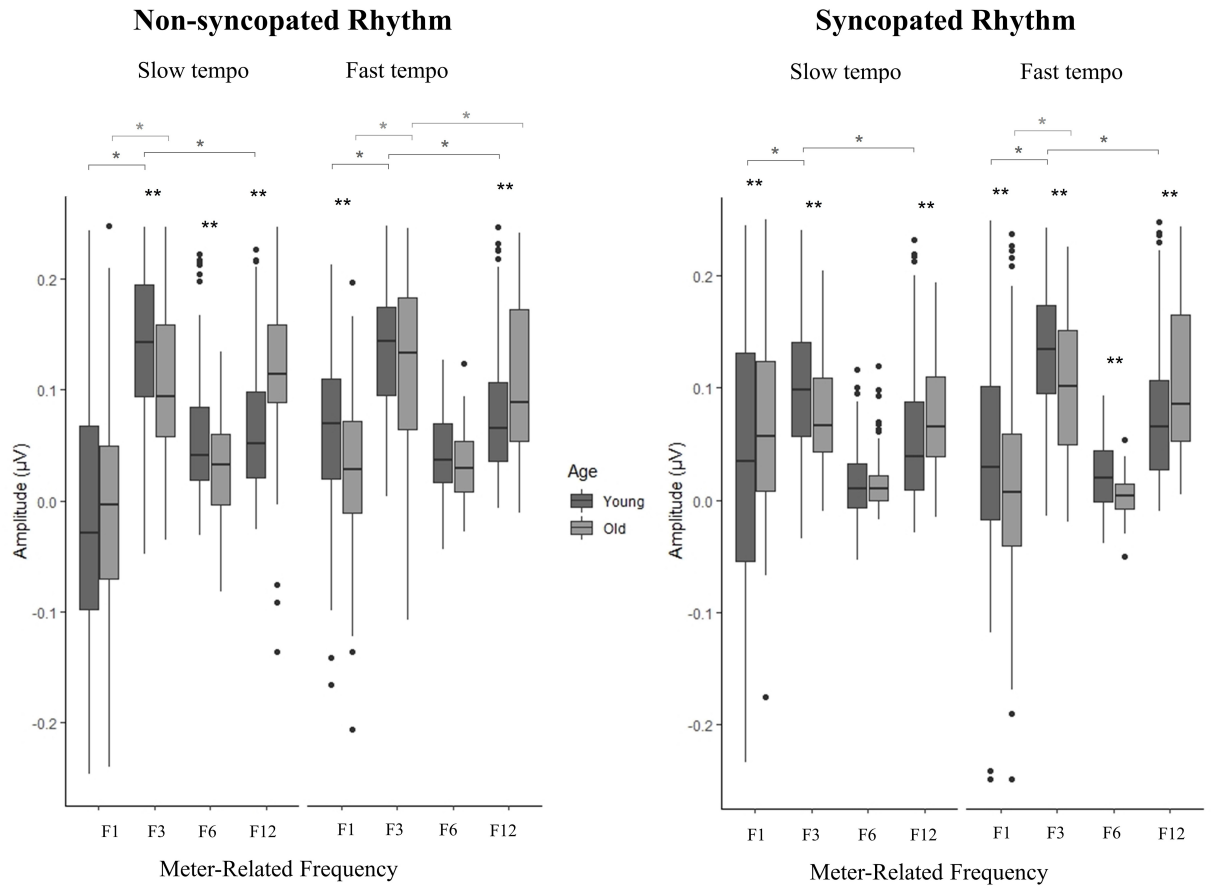

FIGURE 8
Amplitude of neural activity at the different meter-related frequencies across the four conditions. Boxes represent the first quartile, median and third quartile of data, with points representing outliers; data represents amplitude values for each frequency (4 m-related frequencies), channel (12 channels) and participant. $^{**}p < 0.003$ (Bonferroni corrected) for all age comparisons. $^{*}p < 0.006$ (Bonferroni corrected) for all frequency comparisons.

the isochronous sequence, while Sauvé et al. (2019) also included harmonics of that frequency, observing a different pattern of distribution of amplitude across the fundamental frequency of stimulation and its harmonics in older adults compared to younger adults.

In the current study, younger adults demonstrate larger amplitude at F3 compared to F12 in the two rhythms and tempi, in contrast with older adults who do not show such distribution across meter-related frequencies. Sauvé et al. (2019) also observed an overall more equally distributed amplitude across the fundamental frequency and harmonics in older vs. younger adults in the EEG response to an isochronous sound at 1.25 and 2.5 Hz. Since the difference is not modulated by rhythmic complexity, it could be explained by an aspecific change in low-level response to auditory rhythmic inputs, irrespective of meter processing. This is compatible with previous observation of larger N1-P2 evoked potentials elicited in response to auditory stimuli in older adults than younger adults (Anderer et al., 1996; Alain and Woods, 1999; Ross et al., 2009; Zendel and Alain, 2014). As Zendel and Alain (2014, p. 61) explain, "This pattern of results has been attributed to a failure to inhibit irrelevant auditory information as a result of age-related changes in prefrontal functions (Knight et al., 1999; Kok, 1999; Bertoli and Probst, 2005). Evidence for this hypothesis comes from neurological studies showing that patients with lesions in the dorsolateral prefrontal cortex have an enhanced P1 (Alho et al., 1994) and N1 (Knight et al., 1980; Woods and Knight, 1986) amplitude relative to age-matched controls. Hence, the dorsolateral prefrontal cortex appears to play an important role in gating sensory input to the auditory cortex, although the exact mechanisms by which this is achieved remain to be determined. Moreover, the age-related difference in P1 and N1 amplitude was smaller during active compared to passive listening, which suggests that focused attention may mitigate some of the age-related changes in inhibitory function. Finally, it is possible that age-related decline in N2 amplitude was also related to deficits in inhibitory functions

(Čeponienė et al., 2008)." This low-level sensory effect has been linked to reduced adaptation recovery times underlying temporal processing of tone sequences (Herrmann et al., 2016). In the context of this study, it is important to note that the frequencies corresponding to individual acoustic events used to make up the inputs (i.e., frequency F12, corresponding to 200 and 100 ms in slow and fast tempo, respectively) are congruent with the temporal course of typical N1-P2 potentials. Therefore, based on the evidence that older adults generally demonstrate larger N1-P2 amplitudes, it would be expected to find proportionally larger amplitudes at F12 compared to the slower frequency F3 in older adults compared to younger adults, regardless of rhythm complexity and tempo. The approximate wavelength of the N1-P2 complex is 100–200 ms, yielding a frequency of 10 and 5 Hz, respectively. It is therefore possible that the enhancement at these frequencies observed in older adults maps on to the enhanced N1-P2 complex that is typically observed in older adults. In other words, this effect is not related to metrical structure, it only maps onto a particular metrical level in this study. As expected, this effect was found in most conditions, thus suggesting that differences in the shape of the automatic response to auditory stimuli between older and younger adults are likely to explain the differences observed here. This result could also be consistent with the compensation hypothesis of aging, where older adults might increase activity to each single acoustic onset in order to compensate for hearing loss. The relative increase in amplitude at faster vs. slower frequencies observed here in older adults compared to younger adults is the opposite pattern to existing literature (e.g., Clinard et al., 2010; Goossens et al., 2016) and is surprising, given that perceiving and tracking beat subdivisions is more difficult than tracking a beat at fast tempi. One exception is F1 in the slow non-syncopated and syncopated conditions, where older adults have larger amplitudes than younger adults. Here, older adults show enhancement of the whole cycle rate, which may be a different form of compensation. It may also explain that older adults show higher averaged amplitudes of meter-related frequencies than younger adults at slow tempi. Further research is necessary to confirm and investigate these age effects at high and low frequencies in more detail.

Our spatial analysis, however, does not support a compensation theory of aging. In previous literature (Reuter-Lorenz and Cappell, 2008; Halpern et al., 2017), older adults demonstrate activity over a larger surface area in the frontal regions of the brain than younger adults. This pattern is not observed here, suggesting that older adults do not recruit larger neural areas to perform the same task as younger adults overall. Finally, the hypothesized interaction between age and rhythm, where older adults' long-term exposure to Western music may help them compensate for the lack of prominent acoustic feature at meter-related frequencies in the syncopated rhythm was not borne out in our results, suggesting that such experience did not manifest itself in this particular study.

Importantly, the design with fixed order of conditions does not appear to have had a significant effect on our results. If fatigue had been an important factor, we would expect overall neural activity to decrease from one condition to the next. This is not the case, as illustrated by **Figures 3**, **4**, which both present the data in the same order as participants completed blocks, from left to right. However, it is impossible to parse out any potential effects of fatigue. Though this is a disadvantage of a fixed order design, it does have an advantage. Due to the endogenous nature of meter perception, one way to capture indices of the perceived meter is to ask the participants to tap periodically while listening to the rhythm. The participants of this study could successfully perform this task as indicated by the obtained mean and standard deviation of the inter-tap intervals (see **Supplementary material 2** for details), though the tapping sequences were too short to further compare tapping performance across conditions. A fixed order ensures that each participant has received the same amount of "practice" before each condition and therefore has the same opportunity to learn to mentally establish the meter in each condition, which was identified as important in pilot participants. Conversely, while a counterbalanced order design would eliminate any order or fatigue effects, meter perception in each condition may have differed due to more or less experience with the stimuli over time, depending on where the condition occurred in the experiment and was expected to be especially difficult if the fast, syncopated condition was presented first. That being said, the fixed presentation order of the stimuli is indeed a confound, since the neural enhancement to metrical frequencies could be related to the previous non-syncopated condition at the same tempo and the preceding tapping periods involving motor learning of the meter. Future work should explore a counterbalanced design to (i) ensure that the effects reported here are not related to fatigue and (ii) exploit this potential learning effect from the order of the blocks to directly test the link between enhanced neural activity at meter frequencies and the ability to tap the perceived meter. Finally, though tapping data was not the focus of this study, tapping did converge on a tapping rate corresponding to groupings of four events, in line with previous behavioral work (Lenc et al., 2018; Nozaradan et al., 2018a). The impact of aging on sensori-motor synchronization is an important question, and whether tapping on these rhythms is more variable in older participants remains to be investigated with specific designs.

To summarize, this study has demonstrated subtle differences between older and younger adults on neural activity to a rhythmic stimulus. In older adults, we observed preserved selective enhancement of neural activity at meter-related frequencies despite significant hearing loss, even in the syncopated rhythms in which the meter-related frequencies were not prominent acoustic features in the input.

Moreover, younger adults showed lower amplitude at the frequency corresponding to single acoustic events making up the sequences relative to the other, slower meter-related frequencies, which were proportionally larger. In contrast, this difference was reduced in older adults, who showed relatively larger responses at the frequency of single acoustic events compared to activity elicited at slower frequencies. These results are compatible with previous results showing increased amplitude of N1-P2 complexes in response to single acoustic events and indicate that this effect of aging can also affect responses to acoustic events presented in long rhythmic sequences. Future research is necessary to better understand the difference in response shape between younger and 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 human participants were reviewed and approved by Interdisciplinary Committee on Ethics in Human Research at Memorial University of Newfoundland. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SS: formal analysis and writing—original draft, review, and editing. EB: investigation and formal analysis. SN: conceptualization, methodology, and writing—review and editing. BZ: conceptualization, funding acquisition, supervision, resources, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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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/fnagi.2022.848608/full#supplementary-material

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The recognition of time-compressed speech as a function of age in listeners with cochlear implants or normal hearing

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Speech recognition is diminished when a listener has an auditory temporal processing deficit. Such deficits occur in listeners over 65 years old with normal hearing (NH) and with age-related hearing loss, but their source is still unclear. These deficits may be especially apparent when speech occurs at a rapid rate and when a listener is mostly reliant on temporal information to recognize speech, such as when listening with a cochlear implant (CI) or to vocoded speech (a CI simulation). Assessment of the auditory temporal processing abilities of adults with CIs across a wide range of ages should better reveal central or cognitive sources of age-related deficits with rapid speech because CI stimulation bypasses much of the cochlear encoding that is affected by age-related peripheral hearing loss. This study used time-compressed speech at four different degrees of time compression (0, 20, 40, and 60%) to challenge the auditory temporal processing abilities of younger, middle-aged, and older listeners with CIs or with NH. Listeners with NH were presented vocoded speech at four degrees of spectral resolution (unprocessed, 16, 8, and 4 channels). Results showed an interaction between age and degree of time compression. The reduction in speech recognition associated with faster rates of speech was greater for older adults than younger adults. The performance of the middle-aged listeners was more similar to that of the older listeners than to that of the younger listeners, especially at higher degrees of time compression. A measure of cognitive processing speed did not predict

the effects of time compression. These results suggest that central auditory changes related to the aging process are at least partially responsible for the auditory temporal processing deficits seen in older listeners, rather than solely peripheral age-related changes.

KEYWORDS

cochlear implant, time compression, aging, speech perception, temporal processing, fast speech, behavior, hearing loss

Introduction

Cochlear implants (CIs) are auditory prostheses that only convey partial speech information to listeners via a series of electrical pulses across a limited number of electrode contacts. Although this highly distorted rendition of sound is sufficient for most listeners to recognize speech with varying degrees of success in quiet environments (Gifford et al., 2008), real-world listening conditions are frequently less than ideal. While CIs faithfully convey some aspects of acoustic speech, specifically temporal envelope cues, CI processing distorts or eliminates other aspects. Other forms of distortion, such as rapid or time-compressed speech, can result in further deterioration in speech recognition for adults with CIs (Fu et al., 2001; Ji et al., 2013). Recognition of rapid or time-compressed speech is also difficult for older adult listeners with normal hearing (NH) (e.g., Tun, 1998; Gordon-Salant and Fitzgibbons, 2001; Golomb et al., 2007). The age-related difficulty in recognizing rapid or time-compressed speech is at least partially related to deficits in basic auditory temporal processing abilities, such as duration discrimination and gap detection (e.g., Gordon-Salant and Fitzgibbons, 1993; Fitzgibbons and Gordon-Salant, 1996; Gordon-Salant et al., 2006). Thus, there are many types of distortions that can affect speech understanding. Three types of distortion are considered in the present study: distortion imposed by CI sound processing, distortion of the input (rapid speech), and distortion caused by aging neural and cognitive systems responsible for processing temporal speech cues. These distortions have known individual effects on speech recognition; however, how these factors affect older listeners with CIs and interact with each other are as yet unknown.

The first type of distortion, the sound processing of the CI, is inherent to the limitations of the technology. Acoustic sound is processed and transduced by a CI into electrical pulses that are transmitted to the listener's auditory nerve. In this electrical signal, temporal envelope information is largely maintained (Wouters et al., 2015), but temporal fine structure and spectral resolution are greatly reduced (Friesen et al., 2001). With time after activation, a listener with a CI often improves in speech understanding performance (Blamey et al., 2013). Some of this improvement is thought to result from the listener's adaptation to speech that has reduced spectral detail and no temporal fine structure. A simulation of CI-processed speech can be created by eliminating the acoustic fine structure and conveying the temporal envelope using a limited number of channels, as in Friesen et al. (2001). These researchers compared the performance of listeners with CIs and various numbers of electrodes activated to that of listeners with NH and various numbers of channels in simulations of CI-processed speech (i.e., vocoded speech). They found that while CIs typically have 12–24 electrodes, the effective spectral resolution lies between 8 and 10 channels because of the spread of excitation in the cochlea (Friesen et al., 2001). Using vocoded speech allows researchers to present listeners with NH a signal that has been processed in a similar manner to that available to listeners with CIs.

The second type of distortion, rapid or time-compressed speech, disrupts the speech recognition of older listeners with NH more than that of younger listeners with NH (e.g., Konkle et al., 1977; Gordon-Salant and Fitzgibbons, 1993; Tun, 1998; Wingfield et al., 2003). These studies used varying stimuli, from monosyllabic words to complete sentences. In all of them, performance decreased for all listener age groups as the rate of time compression increased. The oldest groups consistently demonstrated larger decreases in performance compared to the younger age groups. As noted above, adults with CIs, both younger and older, also experience difficulty understanding time-compressed speech. Time-compressed speech is not a perfect analog to naturally produced rapid speech. In fact, recognition of time-compressed speech is often better than recognition of naturally produced rapid speech of the same rate (e.g., Gordon-Salant et al., 2014). However, time-compressed speech is a useful tool for examining the effect of temporal rate changes on listeners who rely on the temporal envelope to understand speech. Further, the potential age-related changes in the ability to recognize time-compressed speech in listeners with CIs is not yet known.

The third type of distortion, age-related changes to neural and cognitive mechanisms responsible for processing temporal speech cues, can affect speech recognition when the speech signal is distorted or background noise is present (e.g., Füllgrabe et al., 2015; Babkoff and Fostick, 2017). Age-related declines in speech recognition have been attributed to declines

in peripheral sensitivity, central processing, and/or cognitive abilities (Working Group on Speech Understanding and Aging, 1988). Peripheral hearing loss is prevalent among older adults (Cruickshanks et al., 1998; Lin et al., 2011) and corresponds with declines in speech understanding (e.g., Humes and Dubno, 2010). Age-related reductions in central processing abilities, such as auditory temporal processing, can be linked to age-related changes in the brain, such as reductions in myelination on the auditory nerve and alterations to response properties of neurons (e.g., Gates et al., 2008; Canlon et al., 2010). These central processing changes have been shown to correspond with poorer understanding of speech that is distorted or presented in background noise (e.g., Humes et al., 2012; Presacco et al., 2016). Additionally, cognitive abilities that commonly change with age include reductions in processing speed (Salthouse, 2000), working memory (e.g., Zekveld et al., 2013), and inhibition (e.g., Hasher et al., 1991). Reduced cognitive abilities in these domains have also been linked to poorer speech understanding in background noise (e.g., Rönnberg et al., 2010; Rudner et al., 2011). When relying solely on temporal cues for speech communication, such as when using a CI to hear, it is possible that central and cognitive abilities may be crucial to support speech understanding.

Multiple cognitive abilities, such as working memory and processing speed, have been shown to correlate with the ability of older adults to understand rapid speech (e.g., Wingfield et al., 2003; Vaughan et al., 2006; Dias et al., 2019). Studying the speech perception abilities of older adults with CIs may allow researchers to determine the relative contributions of these cognitive factors to the ability to recognize rapid speech. Several studies have documented improved speech perception with the use of CIs in older adults (e.g., Dillon et al., 2013; Forli et al., 2019; Canfarotta et al., 2020; Murr et al., 2021). Despite the clear benefits of CIs for understanding normal-rate speech in quiet, less is known about the performance of older adults using a CI in more demanding listening situations. Thus, evaluating speech recognition of adults of varying ages who use CIs to recognize challenging speech materials will provide a more realistic picture of the daily communication challenges faced by listeners with CIs, as well as insight into the underlying peripheral, central, and cognitive mechanisms that contribute to these difficulties.

A common issue in previous studies investigating the effect of age on auditory tasks is the confounding factor of peripheral age-related hearing loss. This hearing loss may impact older listeners' performance despite all the listeners having "clinically normal hearing" or "normal hearing for their age" through a certain subset of audiometric frequencies (e.g., Gelfand et al., 1986; Takahashi and Bacon, 1992; Shader et al., 2020b; Lentz et al., 2022). For example, Shader et al. (2020b) reported that the younger listeners with normal hearing had significantly lower (better) thresholds than the older listeners with normal hearing; these hearing acuity differences were the main source of age-related differences in recognition of noise-vocoded sentences. This confound should be reduced by testing listeners with CIs, because the CI bypasses many of the outer, middle, and inner ear sources of age-related hearing loss. In theory, older listeners with CIs are receiving the same peripheral signals as younger listeners with CIs, the main difference being age-related loss of spiral ganglia that could cause differences in neural survival and in the electrode-to-neuron interface (Makary et al., 2011).

If the documented age-related deficit for recognizing time-compressed speech is primarily a result of cochlear hearing loss, then a comparison between younger and older listeners with CIs would not show an age-related deficit, because both groups would be using a device that bypasses cochlear encoding. Alternatively, if the source of the age-related deficit for recognizing time-compressed speech is primarily a result of central auditory or cognitive processing changes, then a comparison between younger and older listeners with CIs would show an age-related deficit similar to that observed for listeners with NH presented with a CI simulation. In other words, older listeners would show the same age-related deficits compared to younger listeners regardless of whether they listen with a CI or to a CI simulation.

The current study was conducted with two listener groups: those who use CIs and those with NH who were presented a CI simulation (vocoded speech). The listeners with NH were included as a control group for comparison to the listeners with CIs, using the same speech materials and time compression methods. Additionally, listeners in both groups were recruited in three age categories (younger, middle-aged, and older) in order to provide insight into the age at which time-compressed speech recognition deficits become apparent and to facilitate

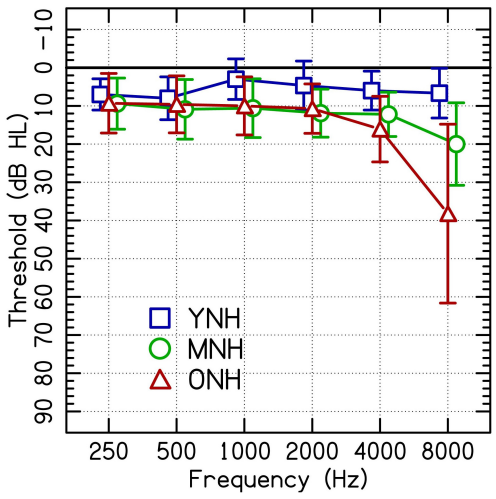

FIGURE 1
Group average audiometric thresholds of the test ears of participating listeners with clinically normal hearing at audiometric frequencies between 250 and 4,000 Hz separated into younger (YNH), middle-aged (MNH), and older (ONH) age groups. Error bars are ± 1 SD.

comparison of the main patterns of performance between the types of listeners (CI, vocoded speech) across the adult age span. The first hypothesis was that there would be age-related decreases in recognizing time-compressed speech by both listeners with CIs and listeners with NH presented with vocoded speech. This age-related decrease in speech recognition was hypothesized to be larger with greater degrees of time compression (i.e., there would be an age group by degree of time compression interaction). The second hypothesis was that faster cognitive processing speed [as measured by the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955)] would be predictive of better performance in recognizing time-compressed speech. Such a result would support the notion that cognitive decline is a significant source of the age-related decrease in recognizing time-compressed speech.

Materials and methods

Listeners

A total of 46 listeners with NH were assigned to one of three groups by age: younger, middle-aged, and older. The younger listeners with NH (YNH; n = 15) were 19–23 years old (M = 20.67, SD = 1.23). The middle-aged listeners with NH (MNH; n = 16) were 52–64 years old (M = 59.75, SD = 2.74). The older listeners with NH (ONH; n = 15) were 65–78 years old (M = 69.79, SD = 4.17). All listeners with NH had thresholds ≤25 dB HL (American National Standards Institute/Acoustical Society of America [ANSI/ASA], 2018) at audiometric test frequencies from 250 to 4,000 Hz in at least the better-hearing ear. See **Figure 1** for audiometric data.

A total of 58 listeners with CIs were also assigned to one of three age groups: younger, middle-aged, and older. The younger listeners with CIs (YCI: n = 16) were 20–48 years old (M = 33.1, SD = 9.35). The middle-aged listeners with CIs (MCI; n = 21) were 50–63 years old (M = 55.1, SD = 4.12). The older listeners with CIs (OCI; n = 21) were 65–82 years old (M = 71.5, SD = 4.85). See **Table 1** for demographic information such as the length of time between when a listener lost usable hearing and implantation (duration of deafness), the duration of implantation, CI processor, and whether the listener mostly learned spoken language before or after implantation.

The age groups were not quite evenly matched. The ages of the younger listeners with NH were significantly lower than the ages of the younger listeners with CIs [$t(15.5) = -5.13$, $p < 0.001$; two-tailed independent samples t-test]. The ages of the middle-aged listeners with NH were significantly higher than the ages of the middle-aged listeners with CIs [$t(34.5) = 4.11$, $p < 0.001$; two-tailed independent samples t-test]. The ages of the older listeners with NH were not significantly different than the ages of the older listeners with CIs [$t(33.2) = -1.16$, $p > 0.05$; two-tailed independent samples t-test]. The well-matched older groups were vital for drawing valid conclusions about the presence or absence of any age-related deficits across listener groups.

Stimuli

The stimuli were Institute of Electrical and Electronic Engineers (IEEE) sentences (Rothauser, 1969) spoken by a male, native speaker of American English. Each sentence has five keywords. Sentences were time-compressed using the PSOLA algorithm in Praat version 5.3.56 (Boersma and Weenink, 2013), which removes minute portions of the waveform at set intervals before condensing the remaining waveform together. This method maintains the speech envelope and many of the pitch characteristics of the original speech. Sentences were compressed by 0% (i.e., no time compression), 20, 40, and 60%. A sentence compressed by 40% has a duration equal to 60% of the original length. At 0% time compression, the talker spoke at an average rate of approximately 3.7 syllables per second. The rate increased to approximately 4.6 syllables per second in the 20% time-compressed sentences, approximately 6.4 syllables per second in the 40% time-compressed sentences, and approximately 10 syllables per second in the 60% time-compressed sentences. These time-compressed sentences were used as the stimuli for the listeners with CIs.

For listeners with normal hearing, the sentences at all four degrees of time compression were also vocoded into 16, 8, and 4 channels using noise vocoding (Shannon et al., 1995). For an n-channel vocoder, pre-emphasis was added to the auditory speech signal using a 1st-order forward Butterworth high-pass filter at 1,200 Hz. The pre-emphasized auditory speech signal was then bandpass filtered using 3rd-order forward-backward Butterworth filters into n logarithmically spaced bands (36 dB/octave) between 200 and 8,000 Hz. The temporal speech envelope from each band was extracted with a Hilbert envelope cutoff of 160 Hz and then used to modulate n noise carriers that were bandpass filtered to match the width of the n logarithmically spaced bands. The 16, 8, or 4 modulated noise carriers were then combined to create the final vocoded output.

Procedure

All procedures were conducted with the informed consent of the listeners and were approved by the Institutional Review Board of the University of Maryland. Listeners were compensated for their time and participation.

Preliminary measures and cognitive assessments

Air conduction thresholds were measured for each NH listener in a sound-treated booth using a Maico MA41

TABLE 1 Demographic information for listeners with CIs.

Subject code	Age (years)	Ear Tested	Duration of deafness (in ear tested) (years)	Duration of implantation (years)	Processor	Onset of hearing loss (Pre-/post-lingual)
Younger listeners with CIs (YCI)						
YCI001	23	R	1	5	Freedom	Post-lingual
YCI002	21	R	3	18	Harmony	Pre-lingual
YCI003	20	R	2	18	N6 (CP910)	Pre-lingual
YCI004	24	L	<1	2	N6 (CP910)	Post-lingual
YCI005	36	L	3	16	N5 (CP810)	Post-lingual
YCI006	41	L	40	1	Naida	Post-lingual
YCI007	41	R	1	1	Naida Q70	Post-lingual
YCI008	42	R	5	14	N5 (CP810)	Post-lingual
YCI009	48	R	<1	0.5	Naida Q70	Post-lingual
YCI010	30	R	<1	28	N6 (CP910)	Post-lingual
YCI011	35	R	<1	1	Sonnet, Rondo	Post-lingual
YCI012	43	L	37	5	N6 (CP910)	Pre-lingual
YCI013	21	R	2	19	Opus 2	Pre-lingual
YCI014	27	R	8	9	N6 (CP910)	Post-lingual
YCI015	45	R	24	21	N6 (CP920)	Pre-lingual
YCI016	32	R	<1	30	N6 (CP910)	Pre-lingual
Middle-aged listeners with CIs (MCI)						
MCI001	56	L	11	5	N6 (CP910)	Post-lingual
MCI002	54	L	2	52	N5 (CP810)	Post-lingual
MCI003	53	L	<1	4	N6 (CP910)	Post-lingual
MCI004	57	R	<1	9	N5 (CP810)	Post-lingual
MCI005	54	L	31	2	N5 (CP810)	Pre-lingual
MCI006	57	L	5	5	N6 (CP920)	Post-lingual
MCI007	61	R	2	4	Kanso (CP950)	Post-lingual
MCI008	55	L	1	2	Rondo, Opus 2	Post-lingual
MCI009	52	R	33	2	Opus 2	Post-lingual
MCI010	56	L	25	6	N6 (CP910)	Post-lingual
MCI011	50	L	10	8	Harmony	Post-lingual
MCI012	50	R	2	11	N5 (CP810)	Post-lingual
MCI013	62	R	13	4	N6 (CP910)	Post-lingual
MCI014	62	L	11	3	N5 (CP810)	Post-lingual
MCI015	63	R	<1	8	Naida Q70	Post-lingual
MCI016	51	L	<1	7	N6 (CP910)	Post-lingual
MCI017	55	R	<1	14	N6 (CP920)	Post-lingual
MCI018	55	L	5	12	Harmony	Post-lingual
MCI019	54	L	6	8	N6 (CP910)	Post-lingual
MCI020	50	R	20	7	N5 (CP810)	Post-lingual
MCI021	50	R	8	2	N5 (CP810)	Post-lingual
Older listeners with CIs (OCI)						
OCI001	71	L	36	20	N5 (CP810)	Post-lingual
OCI002	76	L	7	7	N6 (CP910/920)	Post-lingual
OCI003	65	L	2	10	N6 (CP920)	Post-lingual
OCI004	71	R	4	12	N5 (CP810)	Post-lingual
OCI005	68	R	<1	10	N6 (CP920)	Post-lingual

(Continued)

TABLE 1 (Continued)

Subject code	Age (years)	Ear Tested	Duration of deafness (in ear tested) (years)	Duration of implantation (years)	Processor	Onset of hearing loss (Pre-/post-lingual)
OCI006	70	R	4	8	N6 (CP910)	Post-lingual
OCI007	70	R	<1	5	N5 (CP810)	Post-lingual
OCI008	82	R	2	3	N5 (CP810)	Post-lingual
OCI009	77	L	<1	1	N6 (CP920)	Post-lingual
OCI010	79	R	<1	5	Freedom	Post-lingual
OCI011	65	L	12	8	N6 (CP920)	Post-lingual
OCI012	65	R	5	<1	Naida	Post-lingual
OCI013	70	R	5	4	N5 (CP810)	Post-lingual
OCI014	69	R	12	15	Naida Q70	Post-lingual
OCI015	77	R	1	6	N7 (CP1000)	Post-lingual
OCI016	65	R	8	3	N6 (CP910)	Post-lingual
OCI017	73	R	4	20	Naida Q90	Post-lingual
OCI018	72	R	<1	12	N7 (CP1000)	Post-lingual
OCI019	69	R	<1	7	N5 (CP810)	Post-lingual
OCI020	72	L	<1	4	N6 (CP910)	Post-lingual
OCI021	76	R	29	7	N5 (CP810)	Post-lingual

audiometer and TDH-39 headphones. All listeners completed the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) as a screener for study participation. Listeners with NH had to score 26 or higher (out of 30 possible) in order to proceed, while listeners with CIs had to score 22 or higher because of the confounds of giving a screening in a modality in which the person struggles (Dupuis et al., 2015). Each listener also completed a standardized subtest from the Wechsler Adult Intelligence Scale (WAIS III) (Wechsler, 1955) to measure speed of processing: the Symbol Search test. In the Symbol Search test, two sets of symbols were shown to the listener. The first set consisted of two symbols and the second set consisted of five symbols. The listener had to mark "Yes" if either of the two symbols in the first set were present in the second set and "No" if neither symbol occurred in the second set. They had 2 minutes to complete as many sets as they could. Listeners were instructed to perform the task as quickly and accurately as possible. They were scored on the number of items correctly completed in the allotted time.

Training on vocoded stimuli for listeners with normal hearing

Listeners with NH completed a training phase to familiarize them with vocoded speech. Stimuli used during training were low-context sentences created from a closed set of monosyllabic words. Each sentence contained a name, a verb, a number, an adjective, and a noun. For example, "Pat saw two red bags" or "Jill took five small hats" (Kidd et al., 2008). Sentences were recorded by a male talker at his normal rate of speech and were vocoded following the same procedure as the experimental sentences into 16, 8, or 4 channels. During training, listeners heard three blocks of 15 vocoded sentences drawn randomly from the 16-, 8-, and 4-channel vocoded sentences. Listeners were seated in front of a computer in a double-walled sound-attenuated booth (Industrial Acoustics Inc., Bronx, NY, USA). The sentences were presented through a soundcard (UA-25 EX, Edirol/Roland Corp., Los Angeles, CA, USA) and amplifier (D-75A, Crown Audio, Elkhart, IN, USA) monaurally over circumaural headphones (Sennheiser HD 650, Hanover, Germany). The ear with better hearing was chosen for this experiment, or the right ear if thresholds were the same in the two ears. MATLAB software (MathWorks, Natick, MA, USA) was used to present a five-by-eight grid of words on the computer screen. Each sentence contained one of the eight words from each column. The listener selected the words that they heard in each sentence, guessing if they were unsure. Visual feedback was provided after each trial. After completing the 45 sentences of practice, listeners started the experimental protocol.

Experimental protocol

All listeners were seated comfortably in a sound-attenuating booth (Industrial Acoustics Inc., Bronx, NY, USA). Listeners with normal hearing used circumaural headphones (Sennheiser HD 650, Hanover, Germany) to listen to stimuli presented at 75 dB(A) through a soundcard (UA-25 EX, Edirol/Roland Corp., Los Angeles, CA, USA) and amplifier (D-75A, Crown Audio, Elkhart, IN, USA). Listeners with CIs used their sound processors and a direct audio input cable connected to the output of the soundcard and amplifier to listen to stimuli presented at a comfortable level. If their sound processor did not accommodate direct audio input (as is the case with many of the newer processors), the acoustic signal was presented to listeners

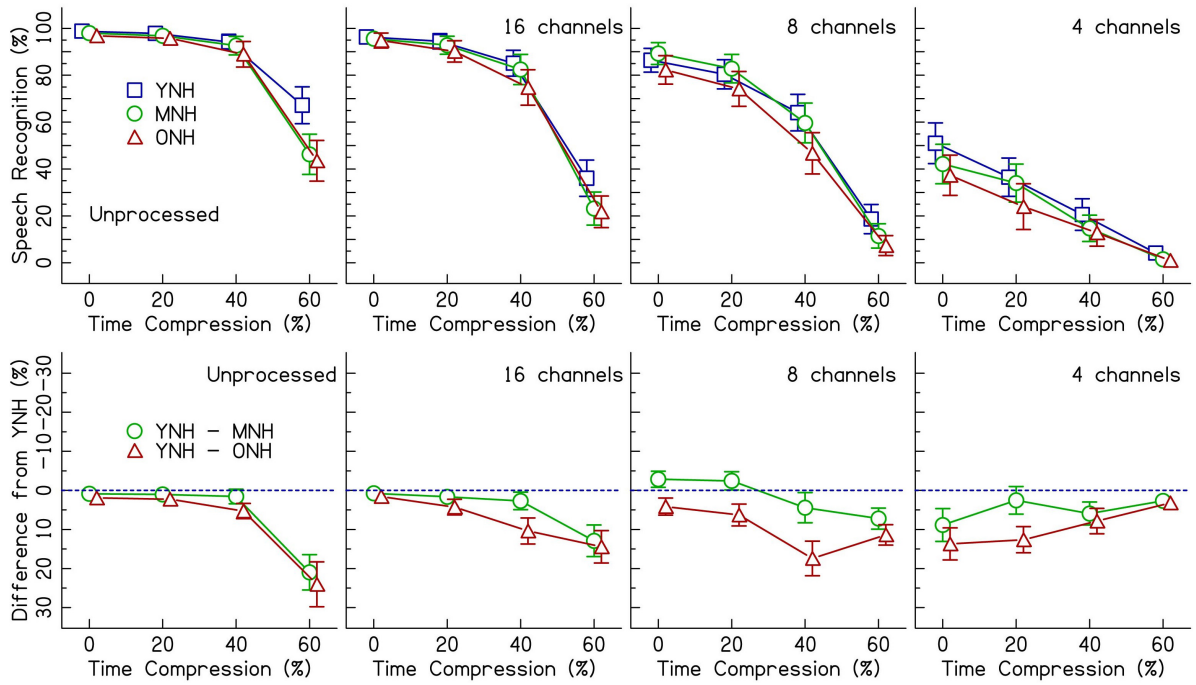

FIGURE 2
The top row shows speech recognition performance in percent correct for listeners with normal hearing (NH) in three age groups (younger, middle-aged, and older) listening to various levels of vocoding (unprocessed, 16-channel, 8-channel, and 4-channel) and four rates of time compression (0, 20, 40, and 60%). Error bars show ± 1 standard error. The bottom row shows the difference from the performance of the younger age group in percent. The dotted blue line represents the performance of the younger listeners. Data points below the line represent worse performance than the younger group. Error bars show ± 1 standard error and are based on 10,000 bootstrapped differences.

with CIs through headphones (Sennheiser HD650s) placed over the processor's microphone. For listeners with normal hearing, five sentences at each of the four degrees of time compression (no compression or 0, 20, 40, and 60%) and the four degrees of vocoding (none or unprocessed, 16 channels, 8 channels, 4 channels) were presented in a random order for a total of 80 sentences in a single block. These listeners heard four blocks with no repeated sentences for a grand total of 320 sentences (20 in each degree of time compression/number of vocoding channels condition). For listeners with CIs, 10 sentences at each degree of time compression in blocks of 40 sentences were presented in random order and without replacement. Listeners with CIs heard four blocks of 40 sentences for a grand total of 160 sentences (40 at each degree of time compression). This is twice the number of sentences heard at each degree of time compression compared to the listeners with NH, but fewer sentences overall because the listeners with NH also completed three vocoded conditions.

Listeners were asked to repeat each sentence aloud and an experimenter in the room marked which of five keywords in each sentence were correct. Listeners were encouraged to guess if they were unsure of a word. No feedback was provided during the experiment. Scoring followed the protocol outlined by Stilp et al. (2010): no penalty was imposed for guessing incorrect words, incorrect word order, or incorrect word endings as long as the pronunciation of the root was unchanged (e.g., "help" was scored as a correct response for "helped" but "drink" was scored as incorrect for "drank"). Guesses that included incorrect word endings without changing the pronunciation of the root were extremely rare.

Analysis

Data were analyzed using generalized linear mixed effects regression modeling with a binomial distribution using the lme4 package version 1.1.27.1 (Bates et al., 2015) in R version 4.1.1 (R Core Team, 2021). These models use trial-by-trial data to predict the (log-odds) probability of a correct response. The dependent variable was the percentage of correct keywords per sentence (out of five). Amount of time compression (four levels: 0, 20, 40, and 60%), number of vocoded channels (four levels: unprocessed, 16, 8, and 4), age group (three levels: younger, middle-aged, and older), and the mean-centered standardized scores from the Symbol Search task were used as the independent variables. One model was fit to the data from the listeners with NH while a separate model was fit to the data from the listeners with CIs. This second model did not

TABLE 2 Logistic mixed-effects model describing the effects of experimental variables and other predictors on speech recognition performance of listeners with NH.

Fixed effects	Log-odds estimate	SE	*z*	*p*	
(Intercept)	5.41	0.21	26.22	< 0.001	***
AgeMNH	−0.23	0.27	−0.86	0.391	
AgeONH	−0.48	0.27	−1.76	0.079	
TC20	−0.53	0.08	−6.58	< 0.001	***
TC40	−1.58	0.08	−19.43	< 0.001	***
TC60	−4.40	0.10	−45.59	< 0.001	***
Channels16	−1.54	0.12	−12.35	< 0.001	***
Channels8	−3.04	0.14	−21.06	< 0.001	***
Channels4	−5.49	0.18	−30.90	< 0.001	***
AgeMNH × TC20	0.01	0.10	0.13	0.894	
AgeONH × TC20	−0.13	0.10	−1.27	0.205	
AgeMNH × TC40	−0.35	0.10	−3.47	< 0.001	***
AgeONH × TC40	−0.49	0.10	−4.80	< 0.001	***
AgeMNH × TC60	−0.96	0.12	−8.27	< 0.001	***
AgeONH × TC60	−0.95	0.12	−7.91	< 0.001	***
AgeMNH × Channels16	0.22	0.16	1.41	0.159	
AgeONH × Channels16	0.17	0.16	1.04	0.299	
AgeMNH × Channels8	0.45	0.19	2.40	0.017	*
AgeONH × Channels8	0.12	0.19	0.65	0.516	
AgeMNH × Channels4	−0.09	0.23	−0.41	0.680	
AgeONH × Channels4	−0.17	0.23	−0.73	0.464	

Random effects	Variance	SD	Correlations							
By-Sentence intercepts	2.58	1.61								
By-Sentence AgeMNH slopes	0.44	0.67	−0.33							
By-Sentence AgeONH slopes	0.39	0.63	−0.28	0.48						
By-Sentence TC20 slopes	0.51	0.71	−0.13	0.11	−0.06					
By-Sentence TC40 slopes	0.79	0.89	−0.40	0.11	0.06	0.49				
By-Sentence TC60 slopes	1.53	1.24	−0.63	0.17	0.21	0.24	0.68			
By-Sentence Channels16 slopes	0.90	0.95	−0.51	−0.03	−0.04	−0.17	0.18	0.17		
By-Sentence Channels8 slopes	1.37	1.17	−0.67	0.18	0.08	−0.12	0.15	0.40	0.75	
By-Sentence Channels4 slopes	2.55	1.60	−0.68	0.14	0.18	−0.10	0.18	0.42	0.61	0.74
By-Listener intercepts	0.43	0.66								
By-Listener Channels16 slopes	0.09	0.31	−0.50							
By-Listener Channels8 slopes	0.17	0.41	−0.74	0.81						
By-Listener Channels4 slopes	0.28	0.53	−0.60	0.82	0.89					

Significant fixed effects are marked with asterisks, with *p*-values generated by Wald z-scores. The intercept estimate represents the predicted log-odds speech recognition performance of the YNH listener group in the 0% time-compressed and unprocessed speech condition, which is used as the reference for all other conditions. The values in the first column of the Correlations reflect the correlation of that row's variable with the intercept. The values in the second column reflect the correlation of that row's variable with the first slope variable under the common intercept. Significance codes: "***" < 0.001; "**" < 0.01; "*" < 0.05.

include the vocoding variable because the listeners with CIs did not listen to any vocoded sentences. A third model was fit to compare listeners with CIs and listeners with NH presented 8-channel vocoded speech–the number of channels associated with the average spectral resolution available to listeners with CIs (Friesen et al., 2001).

Mixed effects models are able to model multiple sources of random variability. This allows the models to explain more variance than simpler fixed effects models (e.g., regression, ANOVA, generalized linear models). The procedure for model building described in Hox et al. (2017) was followed. First, a model with only the random intercepts of listener and sentence was run as a baseline. Then, the independent variables related to the hypotheses were added to the model as fixed terms and interaction terms, including time compression, number of vocoded channels (for the model on the data from listeners with NH), and age group. The Symbol Search scores were not predicted to interact with any of these variables and so this variable was added only as a fixed effect (no interactions). After fitting the model with the predicted fixed effects, random slopes were added to the model. First, a maximal random effects structure was attempted. This included all possible

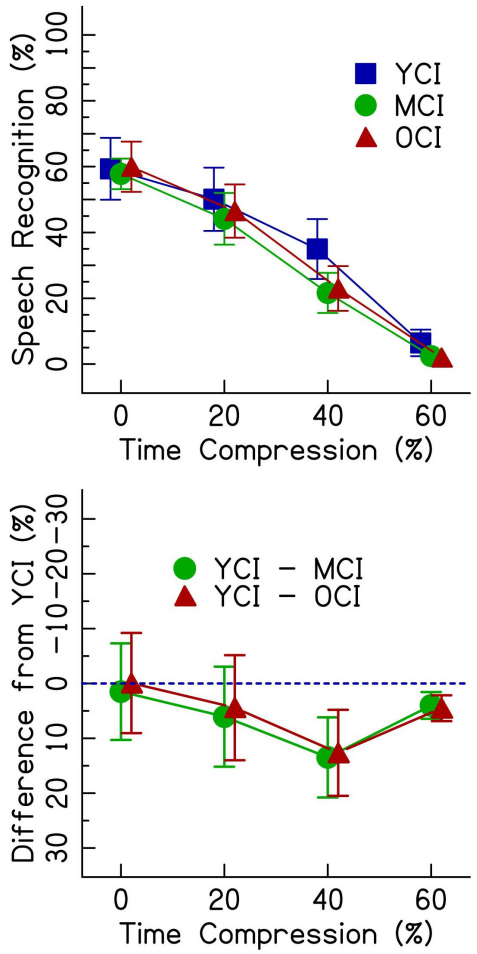

FIGURE 3
The top panel shows speech recognition performance in percent correct for listeners with CIs in three age groups (younger, middle-aged, and older) listening to four rates of time compression (0, 20, 40, and 60%). Error bars show ± 1 standard error. The bottom panel shows the difference from the performance of the younger age group in percent. The dotted blue line represents the performance of the younger listeners. Data points below the line represent worse performance than the younger group. Error bars show ± 1 standard error and are based on 10,000 bootstrapped differences and the smallest group size of 16.

slopes and interactions: time compression and number of vocoding channels on the listener intercept and age group, time compression, and number of vocoding channels on the sentence intercept. If it converged, each model version was compared to previous iterations using a Likelihood Ratio Test. A systematic trial of all possible combinations identified the model with the lowest Akaike Information Criterion (AIC) and the maximal random effects structure that still converged, as suggested by Barr et al. (2013). This maximal converging model then underwent stepwise backward elimination, first eliminating non-significant interaction terms until the terms that remained were either significant themselves or contributed to a significant interaction. The reduced model was presented if a Likelihood Ratio Test showed it to be a significantly better fit to the data than the maximal model.

Results

Listeners with normal hearing presented vocoded speech

Figure 2 (top row) shows speech recognition performance for listeners with NH across increasing rates of time compression. Each panel displays the performance when listening to different CI simulations. Age-related differences are best observed in the bottom row of Figure 2. The performance of the middle-aged and older groups is plotted as a difference (in percent correct) from the performance of the younger group–represented by the dotted line. Performance was at ceiling for unprocessed speech in the 0 and 20% time-compressed conditions and declined beginning at 40% time compression. With 60% time compression, the performance of the MNH and ONH listeners declined even further. The decline in performance for the middle-aged and older listeners appears to be larger than the decline in performance for YNH listeners as shown in the top row of the figure. Similar age-related declines for recognition of time-compressed speech by MNH and ONH listeners, relative to YNH listeners, were observed when speech was vocoded with 16 and 8 channels. In the 4-channel vocoded condition, performance was at floor for 60% time-compressed speech. Overall, speech recognition performance decreased as the number of vocoder channels decreased.

Results from the generalized linear mixed effects model on the trial-by-trial data from the listeners with NH are shown in Table 2. The intercept estimate represents the predicted log-odds speech recognition performance of the YNH listener group in the 0% time-compressed and unprocessed speech condition. The other values listed in the table are the changes in performance for the given variables from the reference group (YNH) and the reference conditions (unprocessed and 0% time compression). The analysis revealed significant interactions between age group and time compression. The significance of these interactions was driven by the differences in performance at 40 and 60% time compression between the YNH group and both the MNH and ONH groups. Both of the older listener groups performed more poorly than the younger group at these degrees of time compression. To determine if there was a significant difference between the MNH and ONH groups, the model was releveled with the MNH group as the reference. There were no significant differences in performance between the MNH and ONH groups for 40 and 60% time-compressed speech or overall (all p's > 0.05). In the model presented in Table 2, there were also significant

TABLE 3 Logistic mixed-effects model describing the effects of experimental variables and other predictors on speech recognition performance of listeners with CIs.

Fixed effects	Log-odds estimate	SE	*z*	*p*	
(Intercept)	0.81	0.38	2.12	0.034	*
AgeMCI	−0.48	0.52	−0.93	0.354	
AgeOCI	−0.16	0.50	−0.31	0.757	
TC20	−0.60	0.11	−5.71	< 0.001	***
TC40	−1.87	0.13	−13.95	< 0.001	***
TC60	−4.91	0.29	−17.02	< 0.001	***
AgeMCI × TC20	−0.29	0.14	−2.14	0.032	*
AgeOCI × TC20	−0.24	0.13	−1.79	0.074	
AgeMCI × TC40	−0.61	0.18	−3.45	< 0.001	***
AgeOCI × TC40	−0.74	0.17	−4.27	< 0.001	***
AgeMCI × TC60	−1.07	0.39	−2.74	0.006	**
AgeOCI × TC60	−1.08	0.37	−2.95	0.003	**

Random effects	Variance	SD	Correlations				
By-Sentence intercepts	1.10	1.05					
By-Sentence AgeMCI slopes	0.61	0.78	−0.43				
By-Sentence AgeOCI slopes	0.57	0.75	−0.34	0.67			
By-Sentence TC20 slopes	0.40	0.64	−0.02	0.00	−0.16		
By-Sentence TC40 slopes	0.71	0.84	−0.10	0.08	−0.06	0.30	
By-Sentence TC60 slopes	1.53	1.24	−0.37	0.20	0.05	0.28	0.49
By-Listener intercepts	2.10	1.45					
By-Listener TC20 slopes	0.05	0.22	0.09				
By-Listener TC40 slopes	0.13	0.35	−0.03	0.59			
By-Listener TC60 slopes	0.66	0.81	−0.34	0.31	0.73		

Significant fixed effects are marked with asterisks, with *p*-values generated by Wald z-scores. The intercept estimate represents the predicted log-odds speech recognition performance of the YCI listener group in the 0% time-compressed speech condition, which is used as the reference for all other conditions. The values in the first column of the Correlations reflect the correlation of that row's variable with the intercept. The values in the second column reflect the correlation of that row's variable with the first slope variable under the common intercept. Significance codes: "***" < 0.001; "**" < 0.01; "*" < 0.05.

main effects of vocoding compared to unprocessed speech (all *p*'s < 0.001) and one interaction between 8-channel vocoded speech and the middle-aged listener group. This interaction showed that, on average, the middle-aged group performed better than the younger group with 8-channel vocoded speech (z = 2.40, p = 0.02). There was no significant main effect of Symbol Search scores, no significant interactions between vocoding and time compression, and no significant higher-order interactions (all *p*'s > 0.05). The random intercepts of sentence and listener accounted for some of the variance in the data. Including random slopes for age group, amount of time compression, and number of vocoder channels in a maximal random effects structure as per Barr et al. (2013) improved model fit.

Listeners with cochlear implants

Figure 3 (top panel) shows speech recognition performance for listeners with CIs. Unlike the listeners with NH, performance was not at ceiling for 0% time-compressed speech. All age groups performed with about 60% accuracy for 0% time-compressed speech. Generally, there were greater performance decrements on time-compressed speech for the MCI and OCI listeners compared to the YCI listeners. Age-related differences in performance are best observed in the bottom panel of Figure 3, where the performance of the middle-aged and older groups are shown as the difference from the performance from the younger group–represented by the dotted line. In the 60% time-compressed condition, performance was near the floor. Overall, speech recognition performance decreased as time compression increased. This follows the same general trend as was seen in the performance of listeners with NH.

Results from the generalized linear mixed effects model on the data from the listeners with CIs are shown in Table 3. The analysis revealed significant interactions between age group and time compression. The significance of these interactions was driven by the differences in performance between the YCI group and both the MCI and OCI groups in the time-compressed conditions. Recognition of 20% time-compressed speech was poorer for the MCI group compared to the YCI group (Table 3: AgeMCI × TC20, z = −2.14, p = 0.032). The performance of the OCI group was not significantly different than the YCI group at this time compression ratio (Table 3: AgeOCI × TC20, z = −1.79, p > 0.05). Recognition of 40 and 60% time-compressed speech was poorer for both the

MCI and OCI groups compared to the YCI group (Table 3: AgeMCI × TC40, $z = -3.45$, $p < 0.001$ and AgeOCI × TC40, $z = -4.27$, $p < 0.001$; AgeMCI × TC60, $z = -2.74$, $p = 0.006$ and AgeOCI × TC60, $z = -2.95$, $p = 0.003$). To determine if there was a significant difference between the two older age groups, the model was releveled with the MCI group as the reference. There were no significant differences in performance between the MCI and OCI groups at either 40% time compression ($z = -1.96$, $p > 0.05$) or 60% time compression ($z = -0.94$, $p > 0.05$, analysis summary table not shown). There was no significant main effect of Symbol Search scores ($p > 0.05$).

Comparison between listener groups

Given that the average listener with a CI uses roughly eight channels of spectral resolution (Friesen et al., 2001), the 8-channel vocoding condition was chosen to compare the performance of listeners with NH to that of listeners with CIs. Figure 4 shows speech recognition scores from both listener groups. Results from the generalized linear mixed effects model comparing the performance of the two groups (Table 4) show a main effect of listener group (Table 4: ListenerGroupCI, $z = -7.05$, $p < 0.001$), with listeners with CIs generally performing more poorly than listeners with NH presented with vocoded speech. There were also significant interactions between age groups (middle-aged and older) and the greater degrees of time compression (40 and 60%) (all p's < 0.001). These interactions indicate that for both listener groups, the middle-aged and older listeners' recognition of both the 40 and 60% time-compressed speech was poorer than that of the younger listeners at those time-compression ratios. In addition, there were significant interactions between listener group and all degrees of time compression (all p's < 0.01). These interactions indicate that for all age groups, listeners with CIs recognize time-compressed speech more poorly than listeners with NH. However, these interactions should be interpreted with caution because of the floor effects present in the data and because performance was not matched between the two listener groups in the 0% time-compressed condition. There were no significant listener group × age group interactions (all p's > 0.05). This lack of an interaction between listener group and age group suggests that the age-related differences in recognition of time-compressed speech (i.e., between younger, middle-aged, and older listeners) may be similar in both CI and NH listener groups. There were also no three-way interactions between degree of time compression, age group, and listener group, reinforcing the notion that the interaction between age group and degree of time compression may affect listeners with CIs and with NH in a comparable way and the interaction between listener group and degree of time compression may also be equivalent across all age groups.

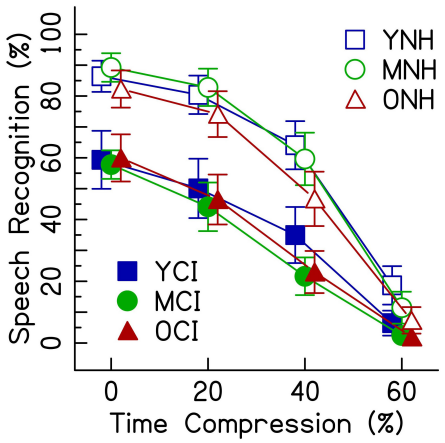

FIGURE 4
Speech recognition performance in percent correct for listeners with CIs and listeners with NH presented 8-channel noise vocoded speech. Each listening group had three age groups (younger, middle-aged, and older) and listened to four rates of time compression (0, 20, 40, and 60%). Error bars show ± 1 standard error.

Discussion

The results of the current study provide insight into the interactions between multiple types of distortion for older listeners with CIs. This study replicated the known separate effects of the distortion of a CI processor, rapid or time-compressed speech, and aging in the central auditory processing system. The results further showed significant interactions between higher degrees of time compression and age. This finding supports the first hypothesis, which was that there would be an age group × degree of time compression interaction for both CI and NH listener groups, specifically that larger age-related decreases would be observed with greater degrees of time compression. The results also showed that scores from a measure of general processing speed did not improve model fit significantly for either listener group (Tables 2, 3), indicating that this measure did not contribute to listener performance. This finding did not support the second hypothesis, which was that faster cognitive processing speed would be predictive of better performance in recognizing time-compressed speech.

Effects of cochlear implant processing and age

Previous research has shown auditory temporal processing deficits in older listeners compared to younger listeners (e.g., Gordon-Salant and Fitzgibbons, 1993; Gordon-Salant et al., 2006, 2007), as well as deficits in understanding time-compressed speech by listeners with CIs (e.g., Fu et al., 2001; Ji et al., 2014). The current study was designed to

TABLE 4 Logistic mixed-effects model describing the effects of experimental variables and other predictors on recognition performance for time-compressed speech by listeners with CIs and listeners with NH presented a simulation of CI-processed speech (8-channel noise vocoding).

Fixed effects	Log-odds estimate	SE	*z*	*p*	
(Intercept)	2.36	0.25	9.55	< 0.001	***
AgeMiddleAged	−0.06	0.29	−0.21	0.837	
AgeOlder	−0.20	0.29	−0.68	0.497	
ListenerGroupCI	−1.68	0.24	−7.05	< 0.001	***
TC20	−0.37	0.10	−3.57	< 0.001	***
TC40	−1.46	0.13	−11.60	< 0.001	***
TC60	−4.26	0.20	−21.47	< 0.001	***
AgeMiddleAged × TC20	−0.21	0.10	−2.01	0.044	*
AgeOlder × TC20	−0.17	0.10	−1.65	0.098	
AgeMiddleAged × TC40	−0.60	0.14	−4.35	< 0.001	***
AgeOlder × TC40	−0.70	0.14	−5.14	< 0.001	***
AgeMiddleAged × TC60	−1.02	0.24	−4.29	< 0.001	***
AgeOlder × TC60	−1.11	0.24	−4.67	< 0.001	***
ListenerGroupCI × TC20	−0.29	0.09	−3.09	0.002	**
ListenerGroupCI × TC40	−0.38	0.12	−3.25	0.001	**
ListenerGroupCI × TC60	−0.60	0.21	−2.89	0.004	**

Random effects	Variance	SD	Correlations					
By-Sentence intercepts	1.19	1.09						
By-Sentence AgeMiddleAged slopes	0.41	0.64	−0.32					
By-Sentence AgeOlder slopes	0.49	0.70	−0.32	0.63				
By-Sentence ListenerGroupCI slopes	0.72	0.85	−0.51	0.06	0.09			
By-Sentence TC20 slopes	0.34	0.58	0.06	−0.06	−0.14	−0.09		
By-Sentence TC40 slopes	0.64	0.80	−0.16	0.00	−0.06	0.05	0.47	
By-Sentence TC60 slopes	1.25	1.12	−0.34	0.04	0.08	0.14	0.14	0.58
By-Listener intercepts	1.24	1.12						
By-Listener TC20 slopes	0.03	0.18	0.08					
By-Listener TC40 slopes	0.14	0.38	−0.14	0.74				
By-Listener TC60 slopes	0.51	0.71	−0.29	0.27	0.71			

Significant fixed effects are marked with asterisks, with *p*-values generated by Wald z-scores. The intercept estimate represents the predicted log-odds speech recognition performance of the YNH listener group in the 0% time-compressed speech condition, which is used as a reference for all other conditions. The values in the first column of the Correlations reflect the correlation of that row's variable with the intercept. The values in the second column reflect the correlation of that row's variable with the first slope variable under the common intercept. Significance codes: "***" < 0.001; "**" < 0.01; "*" < 0.05.

challenge the auditory temporal processing abilities of the listeners and reveal how age-related temporal processing deficits might impact the speech recognition of OCI listeners and/or ONH listeners presented a simulation of CI-processed speech. When speech was presented at a typical rate (the 0% time-compressed conditions) to listeners with NH, speech understanding performance decreased as the number of vocoder channels decreased. However, there were no significant age group effects and no significant age group × number of vocoded channels interactions. While Figure 2 may appear to show a difference between age groups in the 0% time-compressed 4-channel condition, once the random effects of sentences and listeners were added to the model, the difference between age groups in that condition was no longer significant. This indicates that listeners with NH are affected similarly across age groups by the degree of spectral distortion. Listeners with CIs also show no significant differences in performance between age groups when speech is presented at 0% time compression.

The speech understanding scores differ between listeners with NH presented vocoded speech and listeners with CIs (Figure 4). Performance of listeners with CIs was lower than that of the listeners with NH presented with 8-channel vocoded speech and higher than that of the listeners with NH presented with 4-channel vocoded speech. Perhaps a simulation of 6-channel vocoded speech would have better matched performance between the two listener groups. Alternatively, one-to-one matching of listeners by age and performance could be done (Bhargava et al., 2016; Tinnemore et al., 2020). Choosing a simulation that perfectly matches performance, however, is complicated by the differences in experience listening to

spectrally degraded speech, since performance can change over exposure time (e.g., Rosen et al., 1999; Davis et al., 2005; Smalt et al., 2013; Waked et al., 2017). Had the listeners with NH received more practice with vocoded speech than the short training session we provided, the size of the group effects and interactions could have changed.

In theory, the spiral ganglia in the cochlea are the main part of the peripheral auditory system that remain vulnerable to age-related changes and affect speech understanding in listeners with CIs. There are age-related differences in spiral ganglia survival, even in ears with no hair cell loss (Makary et al., 2011). Measures of neural survival in the cochlea, such as electrically evoked compound action potentials, show promise in explaining some of the variance in listener performance with a CI across age groups (e.g., Jahn and Arenberg, 2020; Shader et al., 2020a; Jahn et al., 2021). These measures can provide objective evidence toward the strength or weakness of the electrode-to-neuron interface, which affects the integrity of the signal received by the brain but cannot measure any potential central or cognitive changes. Another factor that affects the electrode-to-neuron interface and speech recognition in listeners with CIs is the placement of the electrode arrays as determined by CT scans (e.g., Berg et al., 2020, 2021). Better simulations that could help match performance between the two listener groups are likely dependent on the stimuli or other individual factors such as array type, insertion depth, and array placement (e.g., Croghan et al., 2017; Berg et al., 2019, 2020). A simulation that accounts for these factors, such as the SPIRAL vocoder (Grange et al., 2017), would allow for more valid comparisons between listener groups.

Effects of time compression and age

As expected, performance decreased with increasing time compression for both listeners with CIs and listeners with NH (**Figures 2**, **3**). The interaction between greater degrees of time compression and age group in each of the three analyses indicates that the middle-aged and older groups recognize time-compressed speech with less accuracy than the younger listeners, regardless of whether they are listening through a CI or to a CI simulation. These results are consistent with previous studies that showed significant interactions between age group and amount of time compression for unprocessed (i.e., non-vocoded) sentences in listeners with NH (e.g., Gordon-Salant and Fitzgibbons, 1993; Tun, 1998) and listeners with age-related hearing loss (Gordon-Salant and Fitzgibbons, 1993).

The current results expand upon previous studies that were conducted with listeners who use CIs. Ji et al. (2013) presented results from 10 listeners with CIs who ranged in age from 24 to 81 years old ($M = 65.2$) and who were presented IEEE sentences that had been 50% time compressed. There was a significant effect of time compression on the speech recognition of these listeners with CIs. The current study expanded the number of listeners and included 58 listeners with CIs who were assigned to one of three age groups with >15 listeners/group (**Table 1**). This allowed the factor of age group to be analyzed as a possible source of variance in listeners with CIs. The current study also varied the degree of time compression and showed interactions between time compression ratio and age group in listeners with CIs, such that the MCI and OCI listeners' recognition of 40 and 60% time-compressed speech was poorer than that of YCI listeners. In conditions with time-compressed speech, the performance of the middle-aged listeners with CIs and with NH presented vocoded speech was consistent with that of the older listeners, rather than appearing at an intermediate range between the younger and older listeners. This suggests that the effects attributed to age are likely affecting the performance of listeners as young as 50 years old (or younger). Together, these results demonstrate that listening to rapid or time-compressed speech through a CI or through spectral degradation similar to that imposed by a CI severely challenges the speech recognition of middle-aged and older listeners.

Effects of cognitive processing speed and age

Contrary to the second hypothesis, cognitive processing speed did not predict recognition of time-compressed speech (**Tables 2**, **3**), and therefore its role in understanding time-compressed speech remains an open question. It was assumed that a measure of cognitive processing speed would affect recognition of time-compressed speech based on previous research (e.g., Wingfield et al., 1985; Dias et al., 2019). Wingfield et al. (1985) showed that word recognition accuracy decreased more for older listeners as speech rate increased than it did for younger listeners and argued that this was evidence of a difference in processing speed. Dias et al. (2019) used the Connections Test (Salthouse et al., 2000) and showed that a derived measure of perceptual processing speed mediated age-related variability in recognition of time-compressed speech. In the current study, non-auditory processing speed was measured directly using the Symbol Search subtest of the WAIS (Wechsler, 1955). Given the current non-significant result, it is possible that general cognitive processing speed may not play a strong role in the recognition of time-compressed speech. Alternatively, it is possible that the measure of processing speed chosen for this study was not sensitive enough to capture subtle cognitive deficits in auditory processing speed that might influence the ability to recognize rapid speech. Future studies should consider alternative measures of cognitive processing speed.

Other cognitive abilities have been shown to affect performance on sentence recognition tasks. Specifically, working memory correlates with measures of auditory temporal

processing, including time-compressed speech (e.g., Vaughan et al., 2006; Humes et al., 2022). Working memory also correlates with performance on distorted speech (e.g., speech in noise) for listeners with hearing impairment (e.g., Rönnberg et al., 2010; Rudner et al., 2011; Zekveld et al., 2013; Füllgrabe et al., 2015). Therefore, another approach would be to assess other cognitive abilities, such as working memory, as predictors of performance on time-compressed speech recognition tasks.

Yet another approach would be an assessment of neural processing of time-compressed speech. Older adults show reduced neural synchrony to normal-rate speech in speech-evoked responses from the brainstem (e.g., Anderson et al., 2012) to the cortex (e.g., Tremblay et al., 2002; Goossens et al., 2016) compared to younger adults. This reduced neural synchrony has been hypothesized to contribute to older adults' difficulties understanding speech in noise (e.g., Aubanel et al., 2016). In the cortex, the timescale of neural oscillations may be related to linguistic processing (e.g., Greenberg, 1999; Ghitza and Greenberg, 2009; Giraud and Poeppel, 2012; Peelle and Davis, 2012) since individual neurons can adapt to small changes in the rate of speech (e.g., Lerner et al., 2014). In addition, neural oscillations may adapt better to naturally rapid speech than to time-compressed speech (e.g., Hincapié Casas et al., 2021). A measure of the accuracy of a listener's neurons to track acoustic modulation in speech may better predict performance on time-compressed speech than measures of cognition.

Other limitations and future directions

Listeners in the current study with NH were designated as having NH based on thresholds at octave frequencies up to 4,000 Hz. The speech stimuli used in the study contained frequencies above 4,000 Hz. Both the MNH and the ONH groups had significantly poorer thresholds than the younger listeners at 8,000 Hz [**Figure 1**; MNH vs. YNH: $t(27) = -4.7$, $p < 0.001$; ONH vs. YNH: $t(27) = -5.4$, $p < 0.001$]. These differences in hearing thresholds at a frequency outside the range used as criteria for the study could have driven some of the performance differences attributed to age.

Listeners in the CI group included those who were born with acoustic hearing and later acquired significant hearing loss, as well as those who were born with little or no acoustic hearing. Most of this latter group were in the YCI group. As a group, they had lower performance overall, likely due to their altered experience learning language through the distortions of a CI processor (e.g., Kirk and Hill-Brown, 1985; Tye-Murray et al., 1995). The etiologies of hearing loss in the younger age group are also distinct from those in the middle-aged and older groups. While etiology has been shown to affect speech recognition outcomes overall in listeners with CIs (Blamey et al., 2013), it is unknown whether the etiology of hearing loss affects the ability to recognize time-compressed speech.

Future studies might benefit from purposefully recruiting listeners with a more uniform distribution of ages. Better matching of ages and performances across listener groups would increase statistical power and might allow interactions between listener groups and experimental factors to reach significance. In the current study, the effects of time compression and age were not significantly different in listeners with NH or CIs. Alternatively, there could be other latent variables in the demographics or listener characteristics that could contribute to variation in temporal processing abilities between listening to vocoded speech and listening with a CI (e.g., years of education, history of noise exposure, years of musical training).

The current study did not directly measure basic non-speech central auditory temporal processing abilities of the listeners, leaving their potential contributions to be inferred. The current study also did not eliminate the possibility that age-related central changes could be caused by peripheral hearing loss that might have occurred before implantation in several listeners in the OCI group. The cause of central auditory deficits cannot be determined solely from performance on a perceptual task, such as that described in the current study. The explanatory power of central auditory processing or electrophysiology measures compared to cognitive predictors could provide additional insight into the source, or combination of sources, of the age-related deficits observed in understanding time-compressed speech.

Summary

This study demonstrated that the deficits in speech recognition of older listeners for time-compressed speech may be primarily affected by age-related declines in central auditory processing rather than solely related to peripheral age-related hearing loss. The findings did not support the notion that the cognitive domain of processing speed contributes to age-related declines in recognition of time-compressed speech. While performance was affected by the degradation introduced to the speech signal by the CI sound processor and the CI simulations, there was no difference between age groups for normal-rate speech. The interactions between age group and time compression highlight the challenge of understanding rapid speech, especially for older listeners. The older and middle age groups showed similar performances, regardless of the mode of listening (acoustic or with a CI), indicating that potential age-related differences in central auditory processing may affect performance by adults prior to 65 years of age.

The similarities in the effects of time compression on both listeners with CIs and listeners with NH suggest a common

source of the deficits associated with older listeners' recognition of time-compressed speech. Even without vocoding, there was a significant effect of greater degrees of time compression on the speech recognition performance of ONH listeners. Given the vast differences in the acoustic signal between unprocessed speech and noise-band vocoded speech, and the similarities in performance between listeners with NH and those with CIs, it appears that the oft-reported deficits in recognition of time-compressed speech exhibited by ONH acoustic-hearing listeners may be at least partially explained by central auditory processing abilities.

Data availability statement

The original contributions presented in this study are publicly available. This data can be found here: https://osf.io/zvb7u/, doi: 10.17605/OSF.IO/ZVB7U.

Ethics statement

All procedures were conducted with the informed consent of the listeners and were approved by the Institutional Review Board of the University of Maryland. Listeners were compensated for their time and participation.

Author contributions

AT collected the data, performed the analyses, and drafted the manuscript. LM helped design the study, collected the data, and wrote an early draft. SG-S helped design the study and contributed significantly to manuscript preparation. MG designed the study, programmed the experiment, oversaw data collection, obtained funding for the study, and provided extensive edits to all versions of the manuscript. All authors contributed to the article and approved the submitted version.

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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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BRIEF RESEARCH REPORT
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Immediate Effects of (Simulated) Age-Related Hearing Loss on Cognitive Processing and Performance for the Backward-Digit-Span Task

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The recall of auditorily presented sequences of digits in reverse order (also known as the Backward Digit Span, BDS) is considered to reflect a person's information storage and processing abilities which have been linked to speech-in-noise intelligibility. However, especially in aging research and audiology, persons who are administered the BDS task are often affected by hearing loss (HL). If uncorrected, HL can have immediate assessment-format-related effects on cognitive-test performance and can result, in the long term, in neuroplastic changes impacting cognitive functioning. In the present study, an impairment-simulation approach, mimicking mild-to-moderate age-related HLs typical for persons aged 65, 75, and 85 years, was used in 19 young normal-hearing participants to evaluate the impact of HL on cognitive performance and the cognitive processes probed by the BDS task. Participants completed the BDS task in several listening conditions, as well as several commonly used visual tests of short-term and working memory. The results indicated that BDS performance was impaired by a simulated HL representing that of persons aged 75 years and above. In the normal-hearing condition, BDS performance correlated positively with both performance on tests of short-term memory and performance on tests of working memory. In the listening condition simulating moderate HL (as experienced by the average 85-year-old person), BDS performance only correlated with performance on working-memory tests. In conclusion, simulated (and, by extrapolation, actual) age-related HL negatively affects cognitive-test performance and may change the composition of the cognitive processes associated with the completion of a cognitive task.

Keywords: backward digit span, cognitive assessment, impairment simulation, age-related hearing loss, short-term memory, working memory

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INTRODUCTION

Traditionally, cognitive assessments are employed in the study of normal and pathological cognitive development and aging (Ford et al., 2012; Weintraub et al., 2013; Salthouse, 2019) and for the screening of neurological and behavioral functions and clinical diagnosis (Brandt, 1991; Nasreddine et al., 2005; Larner, 2017). In recent years, cognitive abilities have also been assessed with increasing

frequency in research in speech and hearing sciences and as part of the clinical practice in hearing health care (HHC; Pichora-Fuller and Singh, 2006; Valente et al., 2006; Füllgrabe and Rosen, 2016). Conducting cognitive tests fulfills various purposes for the hearing scientist and the HHC professional. For example, cognitive screening allows the enforcement of cognitive inclusion or exclusion criteria for and the adjustment of hearing and speech-identification assessments on the basis of the cognitive status of the participants (Füllgrabe et al., 2018; Bott et al., 2019; British Society of Audiology, 2021). In addition, cognitive profiling can further the understanding of individual variability in (un)aided speech identification (Humes et al., 2013; Füllgrabe et al., 2015; Nuesse et al., 2018), and help predict benefits associated with different hearing-aid processing features (Lunner et al., 2009; Neher, 2014; Ohlenforst et al., 2016) as part of a more individualized auditory rehabilitation (Kiessling et al., 2003; Kricos, 2006; Pichora-Fuller and Singh, 2006). It is also being debated whether to expand the scope of practice of the HHC professional to include routine cognitive screening of older adults, with the aim of detecting cognitive impairment, providing counselling, and, if indicated by the results, referring to a mental-healthcare professional for diagnostic evaluation (Armero et al., 2017; American Speech-Language-Hearing Association, 2018; Beck et al., 2018).

However, the generalized use of cognitive tests is not viewed uncritically due to potential intrinsic biases, such as cultural, socioeconomic, and educational factors (Parker and Philp, 2004; Crane et al., 2008; Reynolds and Suzuki, 2012). It also has been acknowledged that, in the older population, cognitive performance may be detrimentally affected by the interaction between age-related changes in peripheral sensory functions and the presentation format of the cognitive assessment (Schaie, 2004; Wingfield et al., 2005; Ben-David et al., 2018). Indeed, there is converging evidence that older people with age-related sensorineural hearing loss (HL) score significantly lower than age-matched normal-hearing (NH) controls on a variety of cognitive tasks (McCoy et al., 2005; Dupuis et al., 2015). Yet, the observation of a deficit in cognitive performance in those individuals does not demonstrate the existence of assessment-related auditory biases, as a reduction in cognitive functioning could also be caused by permanent neuroplastic brain changes in response to prolonged sensory deprivation (Schneider and Pichora-Fuller, 2000; Griffiths et al., 2020). In the latter case, the cognitive deficits do indeed have an auditory origin but are not necessarily related to the presentation format of the cognitive assessment.

Supporting evidence that HL has an immediate deleterious effect on cognitive performance due to the auditory format of the cognitive test employed comes from simulation studies in which auditory deficits are temporarily induced in young NH adults for the duration of the cognitive assessment. In most cases, however, only the effect of a reduction in audibility was investigated (Lindenberger et al., 2001; Jorgensen et al., 2016; Gaeta et al., 2019), and, thus, the true size of the auditory bias was likely underestimated. To mimic the impact of a wider range of perceptual consequences of age-related HL (ARHL) on cognitive-test performance, Füllgrabe (2020a) used an HL simulator mimicking not only elevated hearing thresholds but also reduced frequency selectivity and loudness recruitment. In this study, 56 young NH participants were randomly assigned to one of two listening conditions to perform different memory tasks. Compared to the control condition using unprocessed test stimuli, the simulated-HL condition yielded significantly worse performance on all cognitive tasks. However, due to the use of a between-subject design, a possible sampling bias cannot be ruled out.

To corroborate the assumption that cognitive assessments are prone to auditory biases, the main aim of the present study was to replicate the findings of Füllgrabe (2020a), this time using a within-subject design, in which each participant is tested in all listening conditions that were extended to less and more severe levels of simulated HL compared to the study of Füllgrabe. It was hypothesized that memory performance would be worse in listening conditions simulating HL.

A secondary aim of the present study was to explore whether the mental processes probed by a given cognitive task change as a function of the individual characteristics of the person being assessed (e.g., age, hearing status). Using a cognitive task frequently administered in hearing research in conjunction with measures of speech-in-noise identification (Gieseler et al., 2017; Hillyer et al., 2019; Kamerer et al., 2019), St Clair-Thompson (2010) reported evidence that the backward-digit-span (BDS) task can be described as a measure of working memory (WM) in children, while it probes short-term memory (STM) in adults. To investigate the impact of simulated HL on the cognitive processes at work during the completion of the BDS task, participants were administered the BDS task as well as tests of STM and WM, with the aim of computing the correlational strength between performances on the different tasks. It was hypothesized that performance on the BDS task would be differentially associated with performances on the STM and WM tasks in the NH and simulated-HL conditions.

MATERIALS AND METHODS

Participants

Nineteen (nine females) native-English-speaking volunteers were recruited from the undergraduate student population of Loughborough University (United Kingdom). Their ages ranged from 20 to 25 years (mean age = 22.3 years; standard deviation = 1.4). All participants had normal (i.e., $\leq$ 20 dB Hearing Level) audiometric thresholds in the test (i.e., right) ear at octave frequencies between 0.25 and 4 kHz, assessed following the procedure recommended by the British Society of Audiology (2018) and using standard calibrated audiometric equipment. They also had self-reported normal or corrected-to-normal vision.

Stimuli and Procedure

General Procedure

Participants attended a single test session lasting approximately 90 min. After providing demographic and visual-acuity information, and passing the audiometric screen for normal hearing sensitivity, each participant completed five memory

tasks: first, two STM tasks, followed by the BDS task, and, finally, two WM tasks. Short breaks were enforced before and after the BDS task to reduce fatigue. STM and WM tasks were presented visually and in a nearly counterbalanced order across participants. The BDS task was presented auditorily in four listening conditions: first in the "NH condition", and then in three "simulated-HL conditions" presented in a nearly counterbalanced order across participants.

Following the administration of the BDS task, the ability to understand the stimuli in the most severe simulated-HL condition used in the present study (i.e., a moderate HL as experienced by the average 85-year-old person; see Section "Backward-Digit-Span Task and Listening Conditions") was assessed. Participants listened to the stimuli presented in random order and were asked to repeat what they heard. This was done to establish whether performance on the BDS task was affected by the intelligibility of the stimuli.

All testing took part individually in a quiet experimental room at Loughborough University. Participants were seated approximately 70 cm in front of an Apple MacBook Air. For the auditorily presented task, stimuli were delivered through an AudioQuest (California, USA) Dragonfly Red external soundcard and the right earpiece of Sennheiser (Wedemark, Germany) HDA200 headphones, using the open-source audio software Audacity (Version 2.3.3). Consistent with the study of Füllgrabe (2020a), the presentation level for the unprocessed stimuli was set to 70 dB Sound Pressure Level. This corresponds to a raised conversational level which is presumably used by the test administrator when orally presenting stimuli to an older test participant. The same volume setting was used for the listening conditions simulating different levels of severity of HL. For the visually presented tasks, stimuli were displayed in Times New Roman (with a font size of at least 60) on a 13-inch computer screen, using PsychoPy2 (Peirce et al., 2019). At the start of each task, instructions were given verbally by the experimenter. Prior to the administration of the BDS task, participants listened to the stimuli in random order in the simulated-HL condition representing the ARHL of the average 75-year-old person to familiarize them with the degraded stimuli.

The same test format was used for all five memory tasks to facilitate the comparison of performances across tasks. Each task was composed of 14 trials, varying in sequence length from two to eight items to memorize (either digits or letters), with two trials per sequence length. Each task started with a sequence length of two, and then progressed to the next longer sequence. Responses were given verbally by the participants and were scored manually by the experimenter. No feedback as to the correct answer was provided.

Random sequences of digits and letters were generated without replacement using an algorithm implemented in MATLAB (Mathworks, Natick, MA, USA). An additional constraint for digit sequences was that three consecutive digits could not create an easy-to-memorize ascending (e.g., "1-2-3", "2-4-6") or descending (e.g., "6-5-4", "9-7-5") pattern. Two sets of 14 sequences were created for each memory task and used in a nearly counterbalanced order across participants.

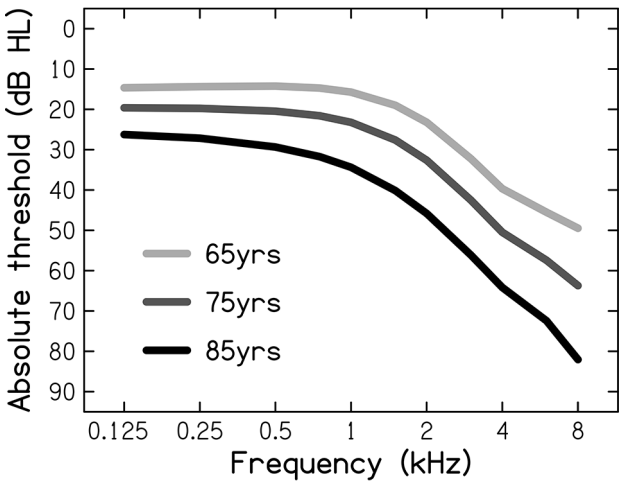

FIGURE 1 | Audiometric thresholds (in dB Hearing Level, dB HL) for the average person aged 65, 75, and 85 years, used as the input for the hearing-loss simulator.

Backward-Digit-Span Task and Listening Conditions

Prior to the study, several utterances of each of the digits "1" to "9" were recorded (using a 44.1-kHz sampling rate and 32-bit quantization) from a female native-British speaker with a standard accent. For each digit, the most naturally sounding utterance without artifacts was selected. All retained utterances were equalized in terms of root-mean-square level, before concatenating them and inserting a 1-s-long silence between utterances to create the auditory signals for the BDS task. The task was to recall all digits of a given sequence in reverse order.

To represent NH, the auditory signals were not further processed. To represent ARHL, the auditory signals were processed through an HL simulator implemented in MATLAB and using an algorithm developed by Nejime and Moore (1997). Based on audiometric thresholds that were used as its input, the HL simulator mimicked some of the perceptual consequences of ARHL: elevated hearing thresholds (by attenuating the frequency components in several frequency bands), reduced frequency selectivity (by spectrally smearing the speech signal; Baer and Moore, 1994), and loudness recruitment (by expanding the range of the speech signal's envelope; Moore and Glasberg, 1993). In the present study, three different audiograms were used (see **Figure 1**), representing the hearing sensitivities of the average 65-, 75-, and 85-year-old person, as based on epidemiological audiometric data (Cruickshanks et al., 1998). These audiograms span the range of mild-to-moderate HLs (Stevens et al., 2013).

Short-Term-Memory Tasks

The Forward Digit Span (FDS) task (Binet and Simon, 1907; Wechsler, 2008) and the Letter Span (LS) task (Kinsbourne, 1974; Kail and Hall, 2001) are long-established standard measures of STM capacity (Richardson, 2007), in which test participants are required to recall, respectively, sequences of digits (here from 1 to 9) and sequences of letters (here B, F, H, J, L, M, Q, R, and S, based on Norris et al., 2019) in the order in which they were presented.

In both tasks, each item to be remembered was displayed on the screen for 1 s, followed by a blank screen for 1 s, before the presentation of the next item.

Working-Memory Tasks

The Operation Span (OS) task (Turner and Engle, 1989; Towse et al., 2000) and the Reading Span (RS) task (Daneman and Carpenter, 1980; Füllgrabe and Rosen, 2016) are widely employed different versions of a complex span task, assumed to measure WM capacity (Conway et al., 2005). Both tasks combine a storage component (i.e., the retention of letters and digits for the OS and RS tasks, respectively) with a processing component (i.e., the verification of the results of mathematical operations and the semantic correctness of sentences in the OS and RS tasks, respectively). In a trial, each item to be memorized (letters or digits) was followed by an item to be processed (equations or sentences). At the end of each trial, participants are required to recall the sequence of letters or digits in the order in which they were presented. The equations and sentences, as well as the timing for the presentation of the items, were taken from Stone and Towse (2015).

Scoring

The same scoring method as that used by Füllgrabe (2020a) was applied to all tasks: a correct response was awarded when the participant recalled correctly the entire sequence of items to be remembered on a given trial, and the score was weighted by the number of items composing the sequence (e.g., correctly recalling all items of a six-item sequence earns a score of 6 while recalling only five items of that sequence earns a score of 0). As all tasks used the same number of trials and the same sequence lengths, the maximum score in all tasks was 70.

Statistical Analysis

All statistical analyses were conducted using SPSS 24 (IBM Corp., Armonk, NY, USA). As a Shapiro-Wilk test revealed that BDS scores for the simulated-HL conditions for the average 75- and 85-year-old person were not normally distributed, non-parametric tests were used to assess the significance of the effect of simulated HL. Differences between listening conditions were assessed using a Friedman test, followed by one-tailed Wilcoxon signed-rank tests. Spearman's rank correlation coefficient was computed to analyze the association between BDS scores and scores obtained on the STM and WM tasks. The significance of the difference between correlation coefficients was assessed based on the two-tailed test described by Lee and Preacher (2013). In the case of multiple comparisons, uncorrected test results are reported, but their significance was confirmed against Holm-Bonferroni corrected significance levels. For all tests, the criterion used for statistical significance was $p < 0.05$.

RESULTS

Intelligibility of Processed Stimuli

All participants were able to identify all nine digits processed to mimic ARHL experienced by the average 85-year-old person. Hence, it can be assumed that the intelligibility of the digits, even though only assessed in the most severe simulated-HL condition, was also perfect (i.e., 100% correct) in the milder simulated-HL conditions in which the BDS task was conducted.

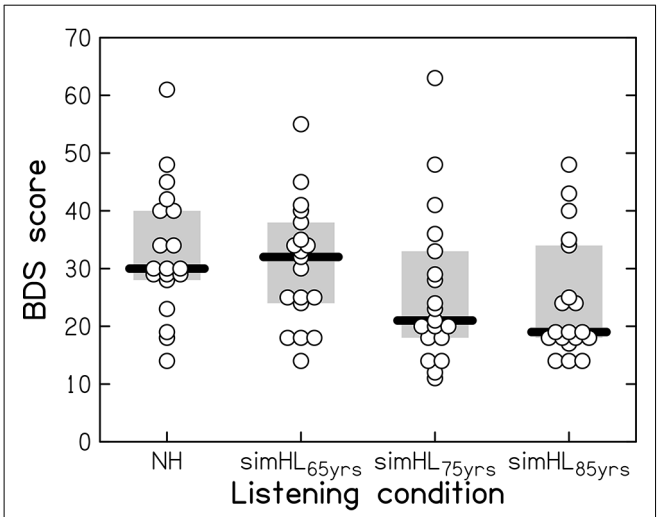

FIGURE 2 | Backward-Digit-Span (BDS) performance (with a maximum score of 70) as a function of listening condition: in the case of normal-hearing (NH) and with three progressively more severe simulated hearing losses, associated with the hearing sensitivity of the average 65-, 75-, and 85-year-old person ($simHL_{65yrs}$, $simHL_{75yrs}$, and $simHL_{85yrs}$, respectively). Horizontal thick bars indicate the median, the light-gray-shaded boxes represent the interquartile range, and the open circles denote individual data points. Overlapping data points are displaced horizontally for better visibility.

Effect of Simulated Hearing Loss on BDS Scores

Performance on the BDS task is shown in **Figure 2** for the four listening conditions: the normal hearing (NH) and the simulated-HL conditions ($simHL_{65yrs}$, $simHL_{75yrs}$, and $simHL_{85yrs}$). The variability of the data was large, even in the unprocessed listening condition. Compared to the NH condition, the $simHL_{65yrs}$ condition yielded similar median BDS performance, while the simulated-HL conditions for the average 75- and 85-year-old person yielded markedly lower median scores (by 9 and 11 points, respectively). Friedman's analysis of variance confirmed that BDS performance differed across listening conditions ($\chi^2_{(3)} = 17.674$, $p < 0.001$). While performance in the $simHL_{65yrs}$ condition was not significantly different from that obtained in the NH condition ($z = -1.089$, $p = 0.145$), the observed declines in the $simHL_{75yrs}$ ($z = -2.789$, $p = 0.002$) and $simHL_{85yrs}$ ($z = -2.943$, $p = 0.001$) conditions were significant. There was no significant difference in BDS performance between the two most severe simulated-HL conditions ($z = -1.166$, $p = 0.128$).

Association Between Performances on the STM and WM Tasks

Results for the four visually presented memory tasks are shown in **Supplementary Figure 1**. Performances on the two simple-span tasks (FDS and LS tasks) and performances on the two complex-span tasks (OP and RS tasks) respectively correlated

strongly and very strongly (ρ = 0.70, $p < 0.001$ for the STM tasks; ρ = 0.81, $p < 0.001$ for the WM tasks). To obtain a more representative and stable estimate of STM and WM capacity for each participant, scores from the two STM tasks and scores from the two WM tasks, respectively, were averaged. The correlation between mean estimates for simple- and complex-span tasks was moderate (ρ = 0.50, p = 0.014).

Association Between Performances on the BDS Task and the STM and WM Tasks

Since simulating the perceptual consequences of ARHL for the average 65-year-old person did not affect median BDS performance (see **Figure 2**), and to reduce the number of statistical tests conducted for the relatively small sample size used in the present study, the association of BDS scores with mean STM and WM scores was investigated only for the two "extreme" listening conditions (i.e., the NH and simHL$_{85yrs}$ conditions; see **Table 1**).

In the NH condition, BDS scores correlated significantly with STM (ρ = 0.66, p = 0.001) and WM scores (ρ = 0.50, p = 0.014); the positive correlation was strong and moderate, respectively. However, the two correlation coefficients did not differ significantly from each other (z = −0.864, p = 0.387). In the simHL$_{85yrs}$ condition, there was a significant strong positive correlation between BDS and WM scores (ρ = 0.77, $p < 0.001$), but the association of BDS scores with STM scores was weak and nonsignificant (ρ = 0.32, p = 0.088); the correlation coefficient involving WM scores was significantly stronger than that involving STM scores (z = 2.458, p = 0.014).

DISCUSSION

The importance of cognition for speech intelligibility seems widely acknowledged in the HHC sector (Rembaud et al., 2017), and there is an increasing call for the use of cognitive tests in audiological practice (Shen et al., 2016; American Speech-Language-Hearing Association, 2018). However, relatively few HHC professionals currently conduct additional cognitive assessments (Rembaud et al., 2017; Raymond et al., 2020). This is possibly the consequence of a lack of clear guidelines as to who should be screened (e.g., the age above which the assessment should be conducted) and the absence of appropriate tests for the screening of patients with sensory impairments. Interestingly, while the awareness that sensory processing abilities can affect cognitive functioning is not new (Rabbitt, 1990; van Boxtel et al., 2000), the distinction between lower cognitive-test performance due to assessment-format-related factors and lower performance due to permanent neuroplastic changes following sensory deprivation is rarely being made, even though both are likely to occur in older people with ARHL.

TABLE 1 | Spearman's rank correlation coefficients for the relationship between listening condition (NH and simHL$_{85yrs}$) for the BDS task and the two other types of memory tasks (STM and WM).

BDS listening condition	STM	WM
NH	0.66**	0.50*
simHL$_{85yrs}$	0.32	0.77***

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

To investigate in isolation the immediate sensory biases occurring during cognitive assessment (and that could be mitigated by adjusted test-administration methods; Dupuis et al., 2015; Shen et al., 2020; Davis, 2021), some studies have adopted an impairment-simulation approach with NH persons (Lindenberger et al., 2001; Jorgensen et al., 2016; Gaeta et al., 2019). Given the decreasing prevalence of audiometrically NH adults with increasing age (Cruickshanks et al., 1998), it can be challenging to recruit a sufficiently large number of participants from this population (Füllgrabe et al., 2015). Therefore, young NH participants were often used, based on the assumption that they constitute a valid model of older NH listeners. As regards the supra-threshold processing deficits implemented in the HL simulator used in the present study, they seem only slightly affected by aging in the absence of elevated audiometric thresholds (Peters and Moore, 1992; Sommers and Humes, 1993; Gifford and Bacon, 2005). Hence, young and older NH participants are presumably impacted in similar ways by the HL simulation used in the present study.

The aim of the present study was to confirm the findings of a previous HL-simulation study, using a more comprehensive simulation of ARHL than the loss of audibility, and a robust experimental design. Consistent with results reported by Füllgrabe (2020a), BDS scores were significantly lower in the simulated HL conditions mimicking the perceptual consequences of HL of the average 75-year-old person and older than in the NH condition. The reduction in performance was not due to compromised intelligibility of the test stimuli. Hence, while for severe cases of HL, the ability to hear the test stimuli is likely the main (and possibly a sufficient) factor for impaired performance on auditory-based cognitive assessments, it is not a necessary condition, as cognitive performance may be affected even when intelligibility is perfect (Nittrouer and Lowenstein, 2014; Füllgrabe, 2020a). This could be explained by the existence of age- and HL-related deficits in supra-threshold auditory processing abilities (Füllgrabe and Moore, 2018; Ozmeral et al., 2018; Anderson and Karawani, 2020) which have been shown to be associated with speech identification (Lorenzi et al., 2006; Bernstein et al., 2013; Füllgrabe et al., 2015). In case of reduced intelligibility and/or supra-threshold auditory processing abilities, lower cognitive-test performance could be due to additional perceptual efforts being required to achieve speech understanding, thereby reducing the amount of cognitive resource available for the execution of the cognitive task itself (Rabbitt, 1991; Wingfield et al., 2005).

No significant decline in performance was observed for the mildest ARHL simulated in the present study. This could be interpreted as indicating that the cognitive-test performance of persons aged below 75 years is not affected by ARHL. However, performance on the Hopkins Verbal Learning Test, a different memory task requiring the immediate verbal recall of lists of words, has been shown to be significantly reduced by simulated HL representative of a person as young as 70 years (Füllgrabe, under revision). Hence, while establishing a cutoff below which cognitive-test performance is not affected would certainly be

desirable for clinicians and researchers alike, it is likely that its exact value depends on the specific cognitive task being used.

There was no further reduction in memory performance when simulating the most severe level of ARHL used in the present study (corresponding to a moderate HL). This was possibly due to the apparently high difficulty level of the BDS task, as floor effects were observed for some of the participants already for the milder simulated-HL conditions.

Previously (Füllgrabe, 2020a, under revision) and in the present study, the different simulated-HL conditions were defined relative to age-group-specific epidemiological audiometric data (Cruickshanks et al., 1998). This was done with clinicians and researchers in mind who only have access to the test person's age but not their hearing sensitivity. However, given that these age-referenced listening conditions rely on average audiometric data, predicting an auditory bias for individual test participants based on their chronological age is only approximate. To derive clinical recommendations as to which individual might be at risk of being cognitively mis-assessed, a more appropriate approach would be to investigate the impact on cognitive processing and performance of different levels of HL severity defined by audiometric boundaries and audiometric shape (Bisgaard et al., 2010; Cruickshanks et al., 2020).

After averaging performances within each type of memory task (i.e., simple vs. complex measures), mean STM and WM performances correlated only moderately, consistent with the notion that either partly different subcomponent processes are at play when completing the two tasks (as observed in children; Kail and Hall, 2001), or that the same subcomponent processes are used to different extents (Unsworth and Engle, 2007). Performance on the BDS task presented in the unprocessed listening condition correlated moderately and similarly with STM and WM performances, indicating that cognitive processes required for the two visually presented types of memory tasks are also used by NH persons when completing an auditory version of the BDS task. On the other hand, performance on the BDS task presented in the most severe HL condition simulated here (i.e., the $simHL_{85yrs}$ condition) was only (but strongly) associated with performance on the WM tasks. In comparison, St Clair-Thompson (2010), using only visually presented memory tasks, found in young adults that performance on the BDS task was more closely related to measures of STM than to measures of WM. In children, however, the opposite trend was observed. This developmental effect was explained by children employing not only storage but also executive-attentional resources for the digit recall in reverse order (Elliot et al., 1997), while, for adults, the tasks is less attentionally demanding and mainly draws on coding and rehearsal processes (Rosen and Engle, 1997). Applying the same reasoning to the present study, it can be speculated that the completion of the BDS tasks required the involvement of additional executive-attentional resources in the moderate simulated-HL condition compared to the NH condition.

The finding of a strong association between BDS scores and scores on the WM tasks in the presence of simulated HL also has practical implications for the joined administration of the FDS and BDS tasks (e.g., as part of the same subtest of the Wechsler Intelligence Scales) to people with HL. Given that the recall in reverse order of sequences of digits is more demanding on WM under HL, BDS performance should probably not be combined with FDS performance into a single score when people with HL are tested, as the two tasks are not tapping the same cognitive processes.

Study Limitations

Several additional caveats regarding the reported findings should be noted:

A relatively small sample size was used in the present study. Nevertheless, the study's main finding of a significant effect of simulated HL on cognitive-test performance is at least qualitatively consistent with results from previous simulation studies (Jorgensen et al., 2016; Wong et al., 2019; Füllgrabe, 2020a, under revision). In contrast, the conclusion drawn from the correlational analyses that different cognitive processes may be at play during the execution of the BDS task by adults with and without ARHL needs to be considered with caution until a replication of the results is reported for a larger sample.

Participants were not given any practice on the cognitive tasks prior to their administration. This might explain the large interindividual variability in memory performance and floor effects in some of the simulated-HL conditions. The provision of training items would probably reduce any procedural difficulties with the task but is generally not included in clinical cognitive assessments (e.g., Wechsler Adult Intelligence Scale; Wechsler, 2008).

The HL simulator only mimicked some of the perceptual consequences of ARHL. Other auditory processing deficits (e.g., a reduction in sensitivity to temporal cues; Füllgrabe, 2013; Wallaert et al., 2016) related to age- and HL-related changes (e.g., synaptopathy, reduced function of the stria vascularis; Liberman and Kujawa, 2017; Heeringa and Köppl, 2019) were not simulated. Thus, the true size of the auditory bias in cognitive assessment is probably larger than that reported here.

Only the effect of simulated HL on a single cognitive test that requires the processing of auditorily presented stimuli was investigated. Intuitively, an auditory bias would not be expected for cognitive tasks using test stimuli that are presented in other sensory modalities (e.g., visual stimuli), and thus the current findings are only applicable to a subset of cognitive tasks. However, in most cognitive assessments, the presentation of the aim and procedure of the task, as well as specific test instructions, are given orally. Since HL affects the comprehension of speech in general and of instructions in particular (Henn et al., 2017), it is possible that, independently of the presentation format of the test stimuli, cognitive-test performance is affected by HL.

CONCLUSIONS

The cognitive processes involved in the completion of the auditorily presented BDS task and the performance on this task are affected by the simulated (and presumably actual) hearing abilities of the test participant. Ensuring good intelligibility of the test stimuli may not eliminate this bias. This calls into question the validity of the assumption that cognitive assessments provide a sensory-bias-free and process-stable estimate of cognitive

functioning. In the case of auditory cognitive tasks, the hearing abilities of the test participants need to be considered when interpreting the cognitive underpinnings of and the performance on the task in order to avoid the mischaracterization of cognitive functioning (Füllgrabe, 2020a,b).

DATA AVAILABILITY STATEMENT

The dataset analyzed for this study can be obtained from the corresponding author for any research purpose.

ETHICS STATEMENT

The study was approved by the Loughborough University Ethics Approvals (Human Participants) sub-committee (reference number: UG723). Informed written consent was obtained from all participants involved in the study.

AUTHOR CONTRIBUTIONS

CF: conceptualization, formal analysis, writing—original draft preparation, writing—review and editing, visualization, supervision, and project administration. CF and OÖ: methodology, validation, resources, and data curation. OÖ: software and investigation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.912746/full#supplementary-material.

Supplementary Figure 1 | Performance (with a maximum score of 70) for the two short-term-memory tasks (Forward Digit Span, FDS; Letter Span, LS) and the two working-memory tasks (Operation Span, OS; Reading Span, RS). Horizontal thick bars indicate the median, the light-gray-shaded boxes represent the interquartile range, and the open circles denote individual data points. Overlapping data points are displaced horizontally for better visibility.

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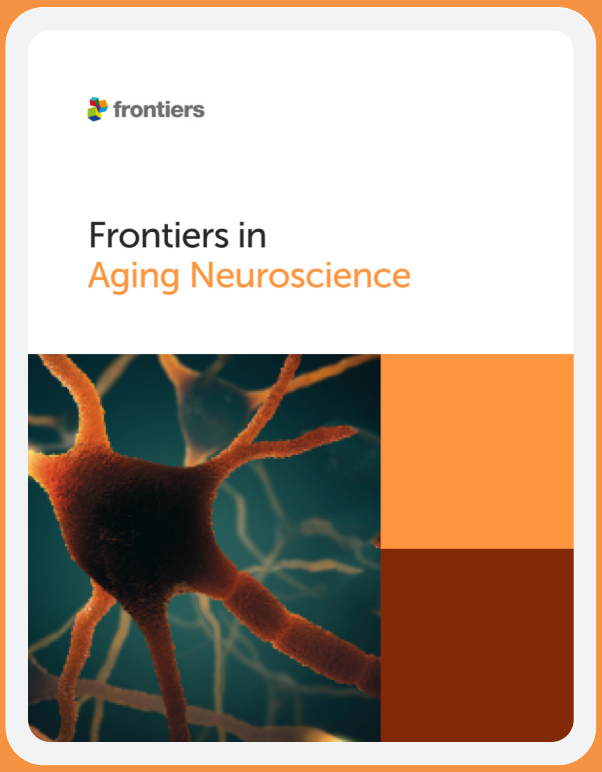

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