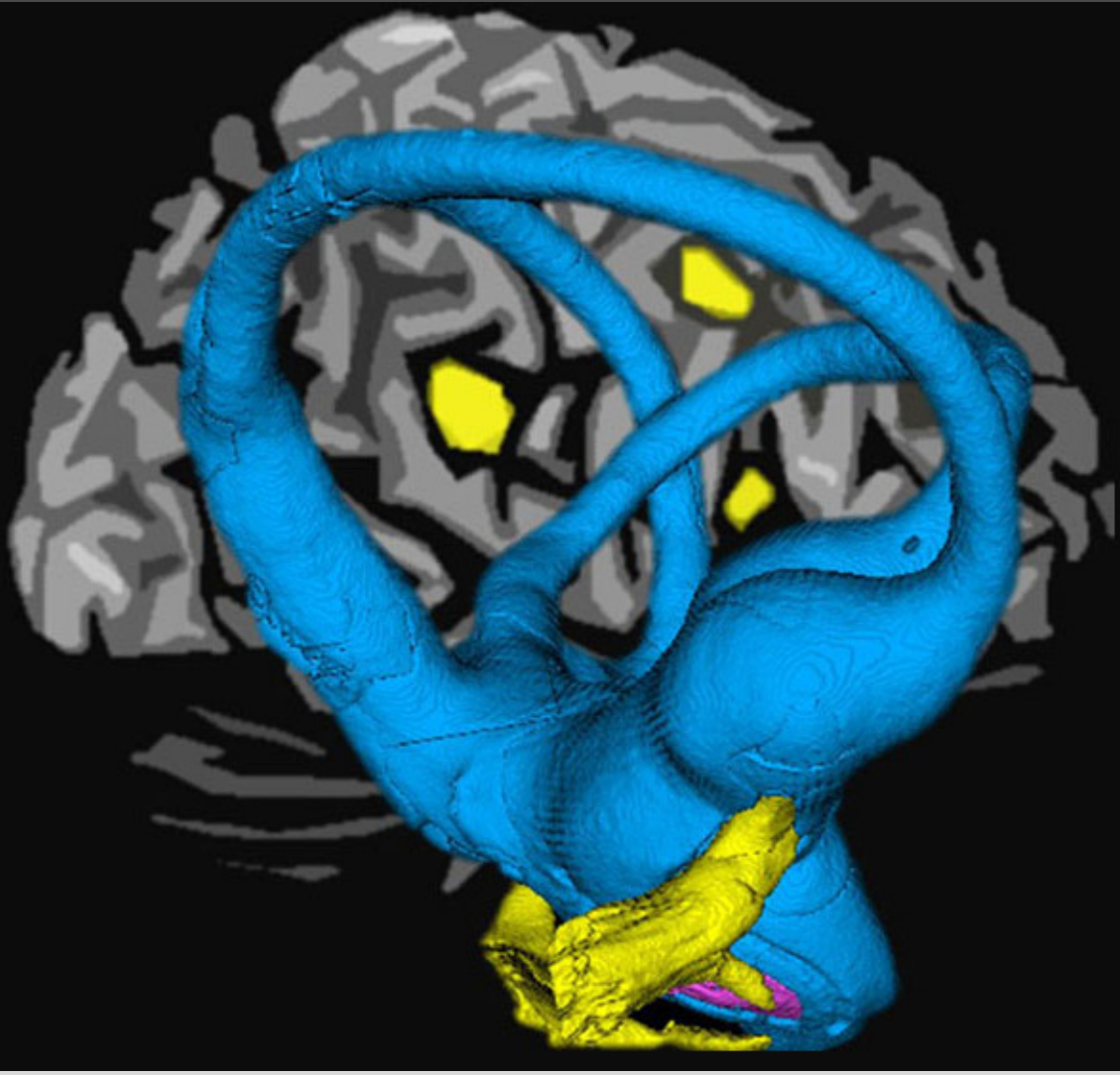
THE VESTIBULAR SYSTEM IN COGNITIVE AND MEMORY PROCESSES IN MAMMALS

EDITED BY: Stéphane Besnard, Christophe Lopez, Thomas Brandt, Pierre Denise and Paul F. Smith

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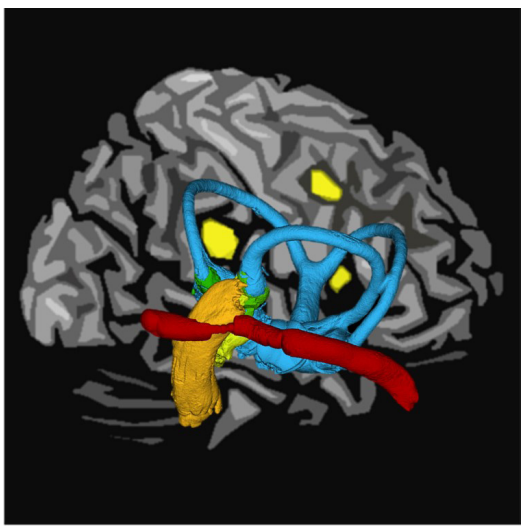
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THE VESTIBULAR SYSTEM IN COGNITIVE AND MEMORY PROCESSES IN MAMMALS

Topic Editors:
Stéphane Besnard, Institut National de la Santé et de la Recherche Médicale U1075, France
Christophe Lopez, Centre National de la Recherche Scientifique, NIA UMR 7260, France
Thomas Brandt, German Center for Vertigo and Balance Disorders, Germany
Pierre Denise, Institut National de la Santé et de la Recherche Médicale U1075, France
Paul F. Smith, University of Otago Medical School, New Zealand



Three-dimensionnal vestibular organ of rat reconstructed from MRI sections projecting on vestibular cortical areas in human. Courtesy of Dr. Martin Hitier and Dr. Christophe Lopez

Since the beginning of life, all plant and animal kingdoms have been developed or modified based on gravity along with atmospheric composition and solar radiation existing on Earth. Gravity is mainly encoded by the otolithic sensors of the vestibular system but its role has been largely underestimated in favor of the exploration of the vestibular semicircular canals and all together reduced to oculomotor and postural coordination. Over the last decade, it has been demonstrated that vestibular sensory information both semi-circular and otolithic organs are crucial in spatial memory processes, body and verticality perceptions in rodent and human supporting entangled functions of balance, orientation and navigation. More recently a role in attention processes has been raised. This topic aims to overview the role and integration of vestibular information in cognitive processes from rodent models to human at the behavioral, imaging and electrophysiological levels.

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EDITORIAL
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Editorial: The Vestibular System in Cognitive and Memory Processes in Mammalians

Stéphane Besnard[1], Christophe Lopez[2], Thomas Brandt[3], Pierre Denise[1] and Paul F. Smith[4]*

[1] COMETE, Institut National de la Santé et de la Recherche Médicale U1075, Normandy University, Caen, France, [2] Centre National de la Recherche Scientifique, NIA UMR 7260, Aix Marseille Université, Marseille, France, [3] German Center for Vertigo and Balance Disorders, Munich, Germany, [4] Department of Pharmacology and Toxicology and the Brain Health Research Centre, University of Otago Medical School, Dunedin, New Zealand

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In the nineteenth century Pierre–Jean–Marie Flourens (1825) and Ernst Mach described the vestibular system and its peripheral organs while Robert Barany, rewarded by the Nobel prize in 1914, was the first to investigate vestibular disorders with caloric tests making surgical treatments of the vestibular organ possible. Recently, Graf and Klam (2006) have reminded us that this ancient sensory system appeared more than 500 million years ago. Logically its influence would most likely not be restricted to balance reflexes at the brainstem level; it must have also shaped our brain. The vestibular system is the one sensory organ dedicated to gravity perception, which along with light and oxygen served as a motor of evolution. In the 1950s the groups of Otto–Joachim Grüsser in Germany, Wilder Penfield in Canada, and later the group of Alain Berthoz in France, demonstrated in elegant experiments on awake monkey (Guldin and Grüsser, 1998), epileptic patient (Penfield, 1957), and neurologically-normal human (Lobel et al., 1999) the existence of vestibular projections to the cortex and how they combine with visual and proprioceptive information. An increasing number of researchers, often fervent disciples, have built on these findings to produce a spate of publications that have consolidated the evidence for a sense of verticality and three-dimensional body representations within the vestibular cortical areas. In the 1990s Paul Smith and colleagues examined vestibular processing in the hippocampus and its role in spatial memory. Exploring this topic in the rodent (Smith, 1997), they began to elucidate the secrets and the previously silent functions of the vestibular system. These findings led to increasing clarity about how vestibular degeneration may be related to some aspects of dementia (Previc, 2013), psychiatric diseases (Gurvich et al., 2013), and cognitive impairments in the elderly (Bigelow et al., 2015; Semenov et al., 2015). The research by Marianne Dieterich and Thomas Brandt has examined the bilateral organization of multiple multisensory cortical areas and revealed the vestibular dominance of the non-dominant hemisphere (Dieterich et al., 2003). They addressed the following questions: how is one global percept of motion and orientation in space formed, and does this dominance determine the lateralization of brain function such as handedness (Brandt and Dieterich, 2015)? A vestibular contribution to the most crucial aspects of the human sense of self and self-consciousness has recently been highlighted by neurological and neuroscientific investigations: vestibular signals contribute to the experience that the self is located within the boundaries of the body (Blanke et al., 2004; Lopez et al., 2008) and may even be involved in self-other discrimination and interactions (Lenggenhager and Lopez, 2015).

In this *Frontiers in Integrative Neuroscience* Research Topic initiated by Sidney Simon, twenty-four articles highlight recent discoveries in the field of vestibular cognition, including: (1) Anatomy of the vestibulo-cortical pathways; (2) Spatial navigation and memory; (3) Spatial cognition, bodily and self-motion perception; (4) Vestibular stimulation and rehabilitation; (5) Posture and motor control; (6) Vestibular disorders and compensation; and (7) Development of vestibular function.

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Sidney A. Simon, Duke University, USA

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****Correspondence:***
Stéphane Besnard
besnard-s@phycog.org

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ANATOMY OF THE VESTIBULO-CORTICAL PATHWAYS

A better understanding of the vestibulo-thalamo-cortical pathways and cortical vestibular processing is needed to fully understand the reciprocal interactions between vestibular processing and cognition. Hitier et al. (2014) provide a comprehensive review of the pathways running from the vestibular apparatus to the cortex, with a focus on the vestibulo-hippocampal pathways. Ventre-Dominey (2014) proposes that two separate cortical vestibular subsystems underpin velocity and inertia processing. A better definition of the vestibular cortex is provided on the basis of clinical and neuroimaging investigations in brain-damaged patients by Brandt et al. (2014), and on the basis of electrophysiological investigations in epileptic patients by Hewett and Bartolomei (2013).

SPATIAL NAVIGATION AND MEMORY

Yoder and Taube (2014) and Smith and Zheng (2013) offer a recent overview of the vestibular contribution to spatial learning and navigation through the head direction and place cells and how vestibular information is integrated into higher navigation centers. Jacob et al. (2014) provide a review and original data relating to the role of the entorhinal cortex (EC) in spatial memory. Despite the evidence that place cells in the hippocampus are adversely affected by the loss of vestibular function, there have been no data reported relating to grid cells in the EC. Here the authors present evidence that inactivation of the vestibular system in rats using tetrodotoxin injections results in a decrease in power in velocity-related theta EEG (5–12 Hz) in the EC, suggesting a disruption of grid cell activity. Cullen (2014) reviews the recent evidence that vestibular signals that are transmitted to higher centers of the brain concerned with spatial memory are in fact multi-modal and more complex than previously thought. She discusses the implications of these findings for the analysis of active and passive movements in relation to spatial memory. Interestingly, Previc et al. (2014) point out how vestibular degeneration may contribute to spatial memory impairments and more generally raise the question of the consequences of progressive sensory loss in the elderly.

SPATIAL COGNITION, BODILY, AND SELF-MOTION PERCEPTION

On the basis of recent evidence that vestibular processing is involved in changing the visuo-spatial perspective and in self-other discrimination, Deroualle and Lopez (2014) propose a vestibular contribution to several sensorimotor mechanisms that are important for social cognition. Psychological investigations have recently demonstrated how vestibular information may play a role in spatial cognition like mental imagery, bodily self-consciousness and self-motion perception, including its influences on emotional aspects and mood as reported by Mast et al. (2014), Pfeiffer et al. (2014), and Tremblay et al. (2013), with an overview of the higher cognitive processes of self-consciousness. Mast et al. (2014) also reports how vestibular disorders and some psychiatric symptoms may be entangled, completing the review of Gurvich et al. (2013).

VESTIBULAR STIMULATION AND NEUROLOGICAL REHABILITATION

Caloric (CVS) and galvanic (GVS) vestibular stimulation have long been used to stimulate the vestibular receptors in neurologically normal participants and have been used to improve recovery in stroke patients. Palla and Lenggenhager (2014) review the importance of these methods for studying cognition and Bottini et al. (2013) highlight the relevance of CVS for studying somatosensory perception and bodily awareness. Two clinical applications of CVS and GVS are proposed by Wilkinson and colleagues. Wilkinson et al. (2013) present a series of case reports on the effects of CVS on post-stroke aphasia. They report that daily CVS for four consecutive weeks was associated with a significant improvement in picture and responsive naming, immediately and at a 1 week follow-up, suggesting that CVS may reduce aphasic symptoms. The same group (Wilkinson et al., 2014) also demonstrates that subliminal GVS can improve hemispatial neglect in right hemisphere stroke patients up to 1 month after the application of GVS, providing evidence for long-term therapeutic effects of GVS. Mast et al. (2014) also report beneficial effects of vestibular stimulation on psychiatric disorders, expanding the field of the vestibular sensory therapy.

POSTURE AND MOTOR CONTROL

Lacquaniti et al. (2013) review neuroimaging data that have recently revealed the role of the temporo-parietal junction, insula, and retroinsular cortex in estimating the consequences of gravity for visual perception and motor preparation. In an original research article, Ferrè et al. (2013) describe the influence of GVS on the generation of motor sequences. They show that right cathodal GVS increases the generation of novel motor sequences. Bernard-Demanze et al. (2014) report original research on static and dynamic postural stability in cochlear implant (CI) patients. They demonstrate that, compared to controls, the CI patients exhibit increased postural instability, especially with the eyes closed, and that these deficits persist during dual tasking with visual or auditory memory tasks.

VESTIBULAR DISORDERS AND COMPENSATION

Lopez (2013) reviews the consequences of vestibular disorders for bodily perceptions, the sense of self and self-consciousness. Peripheral vestibular disorders may alter the perceived shape and size of the body, alter the experience of owning the body and evoke the experience that the self is strange, unreal and disembodied. Tighilet et al. (2014) describe the consequences of vestibular deafferentation for the cat histaminergic system and show that plasticity of the histamine H_3 receptors supports vestibular compensation.

DEVELOPMENT OF VESTIBULAR FUNCTIONS

Wiener-Vacher et al. (2013) review the evidence for the importance of vestibular information for hippocampal representations of space and consider the implications of this for the development of spatial navigation and orientation in children, a subject which has been relatively neglected. They hypothesize that the loss of vestibular function before critical stages of development will lead to specific cognitive deficits in humans. Jamon (2014) confirms the existence of critical periods for the adaptation to gravity from rodent models exposed to micro- and hyper-gravity environments and that vestibular graviceptors are calibrated from gravity experience after birth.

Future studies on the vestibular system will certainly continue to bring new neurophysiological and neuropathological findings as well as innovative concepts. Ideas are emerging on the cerebral benefits of vestibular stimulation which might even spread beyond the brain. For example, recent studies report that the vestibular organ can influence bone and muscle remodeling (Vignaux et al., 2015), help synchronize circadian rhythms (Fuller et al., 2002; Martin et al., 2015), and regulate vegetative and postural blood pressure (Normand et al., 1997; Yates et al., 2014).

The sky's the limit for new ideas and developments in vestibular therapy (both pharmacological molecules and physical devices). One only has to consider the limited range of pharmaceuticals now available for treating vertigo and motion sickness to realize the great demand for new strategies. Such ideas include a highly optimized GVS, a centrifuge creating g levels for long-term space missions, GVS for modulating motor hemi-neglect, vestibular compensation, and more generally motor and balance disorders (Rizzo-Sierra et al., 2014; An, 2015), as well as multisensory "virtual" rehabilitation suggested by recent advances in immersive virtual environments.

This *Frontiers in Integrative Neuroscience* Research Topic has given us the opportunity to gather and share the latest findings on cognitive and memory processes related to the vestibular system. Twenty-four articles and at least ninety-four authors, whom we sincerely thank, have contributed to the success of this Research Topic. They have convincingly demonstrated the growing popularity of the vestibular sense organ in the scientific community and pointed to promising topics of future research!

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Static and dynamic posture control in postlingual cochlear implanted patients: effects of dual-tasking, visual and auditory inputs suppression

Laurence Bernard-Demanze[1,2]*, Jacques Léonard[1], Michel Dumitrescu[1], Renaud Meller[2], Jacques Magnan[2] and Michel Lacour[1]

[1] *Integrative and Adaptive Neurosciences Laboratory, UMR 7260 CNRS/Aix-Marseille University, Marseille, France*
[2] *Service d'ORL et Chirurgie de la Face et du Cou, Assistance Publique Hopitaux de marseille, CHU Nord, Marseille, France*

Edited by:
Paul Smith, University of Otago Medical School, New Zealand

Reviewed by:
Pierre-Paul Vidal, Universite Rene Descartes/CNRS, France
Arata Horii, Suita Municipal Hospital, Japan

***Correspondence:**
Laurence Bernard-Demanze, Integrative and Adaptive Neurosciences Laboratory, UMR 7260 CNRS/Aix-Marseille University, Fédération 3C, case B, 3 Place Victor Hugo, 13331 Marseille Cedex 03, France
e-mail: laurence.demanze@univ-amu.fr

Posture control is based on central integration of multisensory inputs, and on internal representation of body orientation in space. This multisensory feedback regulates posture control and continuously updates the internal model of body's position which in turn forwards motor commands adapted to the environmental context and constraints. The peripheral localization of the vestibular system, close to the cochlea, makes vestibular damage possible following cochlear implant (CI) surgery. Impaired vestibular function in CI patients, if any, may have a strong impact on posture stability. The simple postural task of quiet standing is generally paired with cognitive activity in most day life conditions, leading therefore to competition for attentional resources in dual-tasking, and increased risk of fall particularly in patients with impaired vestibular function. This study was aimed at evaluating the effects of postlingual cochlear implantation on posture control in adult deaf patients. Possible impairment of vestibular function was assessed by comparing the postural performance of patients to that of age-matched healthy subjects during a simple postural task performed in static (stable platform) and dynamic (platform in translation) conditions, and during dual-tasking with a visual or auditory memory task. Postural tests were done in eyes open (EO) and eyes closed (EC) conditions, with the CI activated (ON) or not (OFF). Results showed that the postural performance of the CI patients strongly differed from the controls, mainly in the EC condition. The CI patients showed significantly reduced limits of stability and increased postural instability in static conditions. In dynamic conditions, they spent considerably more energy to maintain equilibrium, and their head was stabilized neither in space nor on trunk: they behaved dynamically without vision like an inverted pendulum while the controls showed a whole body rigidification strategy. Hearing (prosthesis on) as well as dual-tasking did not really improve the dynamic postural performance of the CI patients. We conclude that CI patients become strongly visual dependent mainly in challenging postural conditions, a result they have to be awarded of particularly when getting older.

Keywords: posture control, cochlear implanted patients, dual-tasking, visual input, auditory input

INTRODUCTION

The peripheral vestibular system is made of angular (semicircular canals) and linear (otoliths) sensors providing the brain with sensory signals about three-dimensional head rotations and translations. The vestibular signals project to the vestibular nuclei, which in turn project to the spinal cord, the cerebellum, the thalamus, the parieto-insular vestibular cortex and related cortical areas processing the vestibular input. These descending and ascending pathways are known for their functional role in posture control and equilibrium function, gaze stabilization, self-motion perception, and spatial navigation (see Lopez and Blanke, 2011, for review). Location of the peripheral vestibular system in the inner ear, close to the cochlea, makes vestibular damages possible following cochlear implant (CI) surgery, impairing posture control and the patients' quality of life.

The literature on CI surgery and vestibular function is rather conflicting. No significant adverse effects were observed using behavioral tests (walk across and tandem tests), clinical vestibular examination (caloric and rotational chair tests), or subjective evaluation with the dizziness handicap inventory (Kluenter et al., 2009). Very uncommon loss of vestibular function (one patient among eleven) was shown with the head impulse test, a physiologically relevant stimulation able to detect subtle changes in the functioning of individual semicircular canals (Migliaccio et al., 2005). Significant improvement of both static (Kluenter et al., 2010) and dynamic (Buchman et al., 2004) balance were even observed in CI patients, and significant increase in vestibular responsiveness was noted also in CI patients during air-caloric stimulation (Ribári et al., 1999).

A retrospective case review indicates, however, that approximately three-quarters of adults with implants had experienced vertigo and imbalance (Steenerson et al., 2001). The risk of vestibular function loss depends on the CI surgical technique (Todt et al., 2008), and the vestibular deficits *per se* are function of the evaluation method (subjective questionnaires vs. objective measurements of ocular motor or postural responses). Increased postural instability has been attributed to undesirable vestibular system stimulation by the auditory electrical prosthesis (Black et al., 1978). Electrical current spread from the implant device to the vestibular nerve was suggested also by Ito (1998), who reported 18% of CI patients with dizziness when they used their implant device. The risk of damaged vestibular function in CI patients has been estimated to one third (Huygen et al., 1995) or more (Klenzner et al., 2004), up to two thirds (Van den Broek et al., 1993) with the caloric and velocity step tests. A postoperative peripheral vestibular deficit was reported in 40% of CI patients tested with electronystagmography, computerized dynamic posturography and harmonic acceleration testing (Brey et al., 1995). The authors showed a significant drop of the caloric response of the implanted ear for the older patients (over 60 years of age; $N = 10$), no change for the younger group (under 60 years of age; $N = 7$). Postoperatively, 67% of the older patients had positional nystagmus with EC while 30% was found in the younger. In the CI older patients, balance complaints and vestibular rehabilitation were observed more frequently. The older ears should be more prone to permanent injury after CI surgery (Enticott et al., 2006). Vestibular disturbances were attributed to transient canal function impairment in 20% of cases (Vibert et al., 2001).

Although most of these studies were performed during the acute stage of CI surgery and showed a resolution of the vestibular symptoms within days or weeks, some patients exhibited more persistent disturbances of balance. Chronic, persisting dizziness was attributed to saccular impairment (Basta et al., 2008). Histo-pathological data showed that CI surgery did not cause deafferentation at the periphery, but induced cochlear hydrops accompanied by saccular collapse responsible for attacks of vertigo of delayed onset (Handzel et al., 2006). Late-onset postural symptoms were reported by Shoman et al. (2008) less than 10% of their CI patients, and spells of vertigo occurring later than 1 month after CI surgery were observed by Kubo et al. (2001), Ito (1998) in 16 and 8% of their CI patients, respectively. Dizziness after implantation was seen in 39% of the CI patients (Fina et al., 2003), with the majority experiencing delayed, episodic onset of vertigo. These findings suggest that inner ear lesions due to CI surgery can develop gradually and lead to chronic changes in posture control.

The present study was aimed at examining the possible delayed effects of cochlear implantation on posture control in postlingual CI adult patients. The originality of this investigation was to evaluate the role of visual and auditory inputs suppression, and of a concomitant cognitive task (dual-tasking), on both static and dynamic postural performances of CI patients compared to healthy subjects.

MATERIALS AND METHODS

SUBJECTS

Thirteen healthy subjects ($M_{age} = 39.5$ years, $SD_{age} = 9.1$; 6 males and 7 females) and 16 patients with unilateral CI ($M_{age} = 59.7$ years, $SD_{age} = 12.3$; 10 males and 6 females) participated in the experiment. The two groups did not differed in terms of height ($M_{height} = 172.7$ cm, $SD_{height} = 9.5$ for the controls, $M_{height} = 167.9$ cm, $SD_{height} = 8.3$ for the patients), and weight ($M_{weight} = 65.7$ kg, $SD_{weight} = 13.1$ for the controls, $M_{weight} = 72.6$ kg, $SD_{weight} = 13.6$ for the patients). All subjects provided informed consent before their participation. The experimental protocol was approved by the local Ethics Committee (CCPPRB, 2010: Université de Provence) and followed the recommendations of the Helsinki declaration.

All healthy subjects were included on the basis of the following criteria: no previous physical, neurological, or sensory disorders, no medication that might influence their balance or their cognitive performance, no history of falls in the previous 12 months, no postural and gait disorders and no vestibular deficit.

Cochlear implanted (CI) patients had received unilateral cochlear implantation 1–6 years before their participation to the present study. Nine patients had been implanted on the right side and 7 on the left. All cochlear implantations had been performed by Dr Renaud Meller. All patients suffered from deep unilateral deafness (≥90 Db) and 13 among the 16 patients had deep hearing loss on the non-implanted ear also. The mean percentage of hearing loss was 90% on the implantation side, and 5 subjects wore a hearing aid on the controlateral ear. Origin of deafness was either congenital (2 subjects), brutal (6 subjects), or progressive (8 subjects). Almost all patients (14/16) had participated to a post-operative rehabilitation (lip reading: **Table 1**). The background of the CI patients regarding their vestibular status has not been controlled. Only oto-neurological examination (performed before CI surgery) and a questionnaire (done at the moment of the postural investigation) were available. Oto-neurological examination had revealed no vestibular loss with the caloric test. Data from the questionnaire appreciating the possible involvement of CI surgery-induced vestibular damages on the long term showed that few of the CI patients complained of vertigo and postural instability with or without vision, during head movements, in supermarkets (3/16), and with their prosthesis off (2/16). Most of the CI patients reported not being subject to motion sickness (14/16) (**Table 1**).

EXPERIMENTAL PROCEDURE

Evaluation of the postural performance: posturography

All participants were asked to stand quietly on a static/translational platform (Synapsys, Marseille, France) described in a previous paper (Ghulyan et al., 2005), with the feet aligned to the vertical projection of their shoulders. Subjects were tested in static (fixated support) and dynamic [translation in the anteroposterior (AP) direction] conditions, with their eyes open (EO) or their EC, with hearing (prosthesis ON) or without hearing (prosthesis OFF in patients and white noise inside a helmet in healthy subjects), with a concurrent auditory Spatial memory Task (audi ST, prosthesis ON) or visual Spatial memory

Table 1 | Questionnaire on the long term self evaluation of the effects of CI surgery on the day life activity of the CI patients.

Vertigo	Instability					Motion sickness	Lip reading
	Light	Darkness	Head motion	Prosthesis off	Supermarket		
3/16	3/16	3/16	3/16	2/16	3/16	2/16	14/16

The fractions in each column indicates the number of patients among the total population (N = 16) reporting vertigo, instability or motion sickness, and the number of patients submitted to lip reading rehabilitation after CI surgery.

Task (visu ST, prosthesis OFF). The participants did not wear their shoes during the postural tasks.

Static condition. Recordings of 25 s duration were first performed in the light (EO) while the subjects fixated a visual target placed 2.5 m in front of them, at eye level. In the EC condition, they were asked to look at the memorized visual target. In both situations, they were instructed to maintain their balance on the static platform. The limits of stability (prosthesis ON) were measured in EO and EC conditions by asking the subjects to lean as far as possible, circularly, in all directions. They were instructed to lean their whole body without moving the feet, first forward, then to the right, backward, to the left, and again forward, at their own velocity.

Dynamic condition. Recordings of 25 s duration were then used in the dynamic condition. Subjects were asked to keep their balance and to avoid stepping on the platform which moved fore and aft sinusoidally at the 0.5 Hz frequency. The amplitude of the platform translation was 7 cm. The 0.5 Hz sinusoidal translation frequency was chosen on the basis of our previous studies that showed it was both a challenging postural task and a dynamic postural perturbation which did not induce falls in aged healthy subjects (Bernard-Demanze et al., 2009) as well as in compensated unilateral vestibular loss patients (Young et al., 2012). Two experimenters stood just behind the patients to prevent falling in case of equilibrium loss. The prosthesis ON condition always preceded prosthesis OFF.

The postural tests have been done first in the static condition, and then in the dynamic condition. This non-random order was chosen to allow patients to perform all tests without stress, familiarizing them with easier tests before the more challenging tests.

Cognitive tasks

In the cognitive spatial task, subjects performed a multi-step translation on a 3 × 3 cell imaginary grid. From a starting location at the center of the grid, subjects were instructed to move mentally by following the auditory instructions or the visual instructions projected on a screen in front of them (move step by step to the right, to the left, backward, and forward), and to remember their new localization on the grid (cf. Bernard-Demanze et al., 2009). The cognitive task was performed without verbal expression to exclude destabilizing effects related to articulatory processes (Yardley et al., 2001; Dault et al., 2003). At the end of the exercise, subjects were asked to give their answer, but the experimenter provided no indication on the nature (right or wrong) of their performance.

Cognitive pre-tests

Cognitive pre-tests were aimed at evaluating the capacity of the subjects to perform the spatial task and to determine the time-interval between two instructions allowing them to correctly perform each task. During the cognitive pre-tests, the subjects were seated in front of a computer keyboard, and visual or auditory instructions were delivered on the screen or through the computer loudspeakers, respectively. The first instruction was given 5 s after the initiation of the trial. After each instruction, the subjects responded by pressing a button on the keyboard, which triggered the subsequent auditory or visual instruction. A sound indicated the end of the trial.

For each cognitive task (auditory and visual), six trials made up of 20 instructions were performed and each instruction was presented for 500 ms. Each subject's mean inter-stimulus-interval (mean $_{ISI}$) was calculated on the basis of the number of trials (n) performed for each cognitive task according to the formula: mean $_{ISI} = \sum[T - (20 \times 500)/20]_n$ where:

- T was the total duration of the trial, in seconds,
- 20 × 500 ms the total presentation time of the 20 instructions in the trial,
- n the number of trials.

The mean $_{ISI}$ reflected the baseline cognitive abilities of each subject and was taken as the subject's own reference. For both tasks, the subjects had to report the result of their auditory and visual spatial memory calculations at the end of the experimental trial, and the trial was excluded if the result was false. No information regarding scores was provided between trials.

The mean number of trials with correct results was 6/6 in the controls, 5/6 in the CI patients for both auditory and visual spatial tasks. As a rule, CI patients had a significantly increased mean $_{ISI}$ compared to healthy subjects for the auditory ST condition ($p < 0.001$) but not for the visual ST condition ($p > 0.05$).

Cognitive test. During dual-tasking, successive instructions were presented automatically at each subject's own measured mean $_{ISI}$ by condition (audi ST or visu ST). Since the recording time remained constant for all participants, the number of instructions per trial varied from one subject to another, and as such the CI patients received three times the mean number of instructions per trial ($p < 0.0001$) for the auditory ST condition ($N = 37$ vs. 12) and the same number ($p > 0.05$) for the visual ST condition ($N = 11$) compared to the healthy participants. In this way, the cognitive load was as similar as reasonably achievable

between groups and between subjects, and this allowed a more valid inter-group comparison during dual-tasking.

Evaluation of the postural performance: motion analysis

Head and body motion recordings were made along with the postural recordings of the Center of Pressure (CoP) displacements. The head and body positions and their stabilization in space were recorded using a motion analysis system (Codamotion, Charnwood Dynamics, UK) sampled at 100 Hz. Two active markers were located in the infra-orbital and acoustic meatus on one side of the face to denote the Frankfurt plane, and to enable accurate analysis in all three space dimensions (cf. Tardieu et al., 2009). Head angular displacement during platform translation was measured in the X-Y, X-Z, and Y-Z planes. Head position in space was defined as the average of each head angle while head stabilization was defined as the standard deviation of the head angles. The gain of head displacement was computed as the ratio of head motion in space to platform motion.

Four other optical markers were placed on the knees and hips, and two supplementary ones were located on the platform itself. Similar calculations were made to obtain the knee and hip gains. The pattern of gains across the body characterizes the posture control strategy. A gain close to unity at the knees and tending to decrease close to zero at the head indicates a strategy of head stabilization relative to space. In contrast, gains remaining close to 1 for all markers (knees, hips, and head) point to whole-body stabilization over the feet, that is, a "rigidification" strategy (see Young et al., 2012).

DATA ANALYSIS

Postural performance during quiet standing

Displacements of the CoP were used to measure the limits of stability and the postural performance of the subjects. This traditional approach has been complemented by a more accurate non-linear analysis of CoP displacements using the wavelet transformation. The wavelet analysis software (PosturoPro, Framiral, Cannes) provides a time-frequency chart of body sway and a 3D representation of body sway under both static and dynamic conditions (see Lacour et al., 2008). This method gives access to the changes in the frequency components of body sway with time, the third dimension calculated as the decimal logarithm of the spectral power being given on the 3D map by a color code.

Postural performance in static conditions was evaluated through a postural instability index (PII) derived from the wavelet plots (cf. Bernard-Demanze et al., 2009). The PII values were computed for three frequency bands (F1: 0.05–0.5 Hz; F2: 0.5–1.5 Hz; F3: 1.5–10 Hz) corresponding to frequency domains mostly related to vision (F1) and vestibular/somatosensory (F2) contribution to posture control. As a rule, power in the high band (F3) is not present in healthy subjects during quiet standing, but it can be seen with aging, in postural pathologies, and of course in dynamic postural conditions. The PII values were calculated from both the spectral power recorded in a given frequency range, and the total time during which the spectral power of the different body sway frequencies in this given frequency range tend to be canceled by the posture control mechanisms (see Lacour et al., 2008). Indeed, the wavelet plots showed the spectral power for a particular frequency of body sway was not constant over time, but varied and tended to come close to zero. The algorithm used to compute the PII was as follows:

$$\mathrm{PII} = \sum x \sum y \,\mathrm{SP}\,(\mathrm{F1, F2, F3})/\mathrm{TC}\,(\mathrm{F1, F2, F3})$$

where SP and TC are the spectral power (in arbitrary units) and time cancellation (in seconds) for each of the three frequency bands. In healthy adults, the PII value recorded in the eye open condition during quiet standing is close to unity while it is significantly increased (up to 4–5) in pathological cases or in older adults in dual-tasking (Bernard-Demanze et al., 2009).

Postural reactions to linear AP translations

In dynamic condition, the spectral power density was computed for the 0.5 Hz frequency peak, corresponding to the platform translation frequency. The spectral power peak was expressed in arbitrary units, which ranged from 10^3 to 10^9 depending on the nature (static vs. dynamic) of the postural task.

STATISTICAL ANALYSIS

Static condition

Two parameters describing body sway during quiet standing were analyzed: the limits of stability and the PII. The limits of stability parameter was analyzed using repeated-measures analyses of variance (ANOVAs) with "group" (healthy subjects vs. CI patients) as the between-subject factor, and visual condition (EO vs. EC) as within-subject factors. The PII was analyzed using repeated-measures ANOVAs with "group" (healthy subjects vs. CI patients) as the between-subject factor, visual condition (EO vs. EC) and condition (prosthesis ON, prosthesis OFF, audi ST) as within-subject factors. This parameter was also analyzed for the two groups in EO condition with a separate ANOVA with condition (prosthesis ON vs. prosthesis OFF), and cognitive task (audi ST vs. visu ST) as within-subject factors.

Dynamic condition

Separate ANOVAs were applied to dynamic postural control. Postural response to platform sinusoidal translation at the 0.5 Hz stimulus frequency was evaluated by the spectral power peak provided by the wavelet analysis. The gain of the head, hip and knee was computed using measurements from the motion analysis system, by calculating the ratio of the amplitude of displacement of each marker at its specific segmental level to the amplitude of platform displacement.

Results were considered significant for $p < 0.05$.

RESULTS

POSTURAL CONTROL OF THE CI PATIENTS IN STATIC CONDITIONS

The ANOVA performed on the limits of stability showed significant differences between the CI patients and the healthy subjects [$F_{(1,\ 27)} = 34.23$; $p < 0.000001$] in both EO ($p < 0.00001$) and EC ($p < 0.00001$) conditions. The **Figure 1A** illustrates the stability limits recorded in the CI patients (with their prosthesis ON) and in the controls in both EO and EC conditions. The

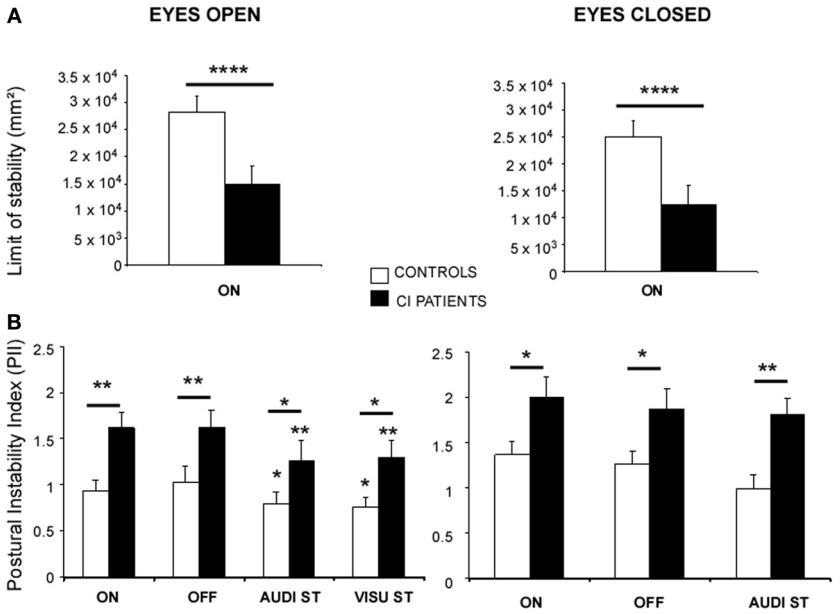


FIGURE 1 | (A,B) Posture control of the CI patients in static conditions. **(A)** Limits of stability of the CI patients (filled histograms) compared to the controls (open histograms) in the eyes open (EO) and eyes closed (EC) conditions. The stability limits are expressed as the energy of the spectral power density recorded in the 0.05–0.5 Hz frequency range while the subjects were standing on the platform and asked to move voluntary as far as possible in the forward/backward and left/right directions, without moving the feet. ****Significant differences ($p < 0.0001$) between the CI patients and the controls. ON indicates that hearing is present. **(B)** Postural Instability Index (PII) calculated from the 3D posturographic map of the center of pressure recordings obtained with the wavelet analysis. Recordings were made in subjects standing quietly on the platform with (EO) or without (EC) vision, with (ON) or without (OFF) hearing, and during dual-tasking (DT) with a concomitant cognitive task consisting of a visual (visu ST) or an auditory (audi ST) memory task. The PII values are expressed on the ordinates; significant differences between the CI patients (filled histograms) and the controls (open histograms) are indicated by asterisks (*$p < 0.05$; **$p < 0.01$).

histograms plot the mean energy recorded in the 0.05–0.5 Hz frequency range while they tilt voluntary their whole body forward, to the left, backward, to the right and again forward. The spectral power density recorded in this low frequency range was significantly reduced by around 50% in the CI patients, indicating that they had reduced voluntary body sways compared to the healthy subjects.

The ANOVA performed on the PII calculated from the whole 3D chart provided by the wavelet transform showed also significant differences between the two groups [$F_{(1, 27)} = 13.56$; $p < 0.001$] in all the experimental conditions tested. The **Figure 1B** illustrates the mean PII values recorded with and without vision (EO and EC), with and without hearing (ON and OFF conditions), and during dual-tasking with the cognitive auditory (audi ST) and visual (visu ST) memory tasks.

As a general rule, modifying the experimental conditions had similar consequences on the postural performance of both controls and CI patients. Suppression of the auditory cues had no effect at all, suppression of visual information increased the PII values ($p < 0.05$), and dual-tasking with the cognitive auditory or visual memory tasks reduced the PII values ($p < 0.05$) compared to the single quiet standing postural task. On the other hand, whatever the postural task, the PII values of the CI patients were significantly increased compared to the controls, indicating that their posture control was not as efficient as in healthy subjects. The two groups differed significantly in the EO condition with and without hearing ($p < 0.01$), and during dual-tasking with the auditory and visual memory tasks [$F_{(2, 24)} = 3.87$; $p < 0.05$; $F_{(2, 30)} = 9.17$; $p < 0.001$, for the controls and the patients, respectively]. The CI patients still differ significantly from the healthy subjects in the EC condition with and without hearing ($p < 0.05$) and during dual-tasking with the auditory memory task ($p < 0.01$).

POSTURAL CONTROL OF THE CI PATIENTS IN DYNAMIC CONDITIONS

In the dynamic condition, the support was translated sinusoidally in the antero-posterior direction at the 0.5 Hz frequency. The ANOVA performed on the spectral power density peak at this stimulus frequency showed that group (CI patients vs. controls), visual condition (EO vs. EC), hearing condition (ON vs. OFF), and dual-tasking (with the auditory memory task) constituted the main fixed effects constituting the sources of variations among the subjects.

The **Figure 2** illustrates the mean spectral power density peaks recorded in these different experimental conditions. The power peaks were not significantly different in the two groups when tested in the EO condition, whatever the experimental condition. In the EC condition, the spectral power density peaks were increased in both groups compared to the condition with vision [$F_{(1, 27)} = 28.86$; $p < 0.0001$]. But the power peaks were drastically increased in the CI patients compared to the controls

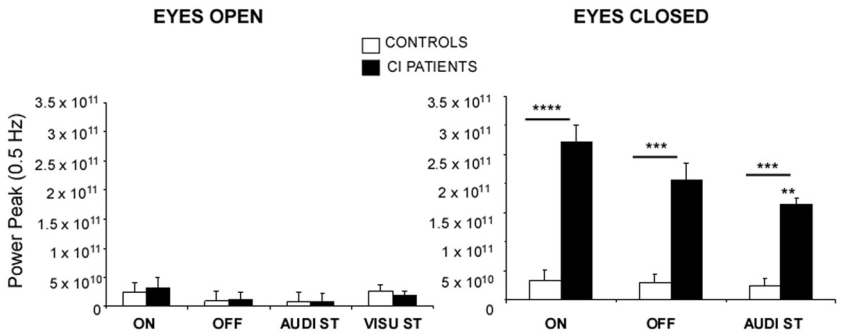


FIGURE 2 | Posture control of the CI patients in dynamic conditions. The spectral power density peaks provide by the wavelet transform at the 0.5 Hz stimulus frequency of sinusoidal platform translation in the for-aft direction are expressed on the ordinates for each of the different experimental conditions: with (EO) or without (EC) vision, with (ON) or without (OFF) hearing, and during dual-tasking with a concomitant cognitive task consisting of a visual (visu ST) or an auditory (audi ST) memory task. Significant differences between the CI patients (filled histograms) and the controls (open histograms) are indicated by asterisks (**$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$). Note the strong impact of eye closure in the CI patients.

$[F_{(1,\ 27)} = 22.73; p < 0.0001]$ in all experimental conditions {ON vs. OFF vs. audi ST: $[F_{(2,\ 54)} = 7.39; p < 0.0001]$}. On the average, the peak amplitude of the spectral power density corresponding to the 0.5 Hz stimulus frequency was 3.1×10^{10} vs. 2.7×10^{11} in the hearing ON condition, 2.8×10^{10} vs. 2.2×10^{11} in the hearing OFF condition, and 2.7×10^{10} vs. 1.8×10^{11} in dual-tasking with the auditory memory task, for the controls and the CI patients, respectively. A significant interaction group × task was found in the EC condition $[F_{(2,\ 54)} = 2.97; p < 0.05]$, the spectral power density peak being decreased in the CI patients during dual-tasking while it remained unchanged in the controls ($p < 0.01$).

The gains of the head, hip and knee displacements with respect to platform displacement are illustrated in the **Figure 3** for all the experimental conditions tested. In the EO condition, the two groups behaved similarly, thus corroborating the data previously shown with the peak of spectral power density. With vision, there was a bottom–up gain decrease from foot to head: the knee gain was close to unity, indicating that the knees (and feet) follow the platform motion, while the gains of the other segments were more and more reduced as far as the head level was concerned $[F_{(2,\ 54)} = 154.84; p < 0.0001]$. These data point to a strategy of head stabilization in space during the for-aft translation of the support. Paradoxically, an interaction group × task was found in the CI patients $[F_{(3,\ 81)} = 8.86; p < 0.0001]$ who showed a poorer head stabilization in space with their prosthesis ON ($p < 0.001$).

This head stabilization strategy was not preserved in both groups in the EC condition (**Figure 3**). The control subjects showed a gain close to unity for all body segments, in all experimental conditions, indicating that they swayed in block with the platform displacement. They exhibited a strategy of head stabilization on trunk, resulting in a rigid whole body translation in space. The CI patients showed on the other hand head stabilization neither in space nor on trunk. They behaved like an inverted pendulum with strongly increased gains at the different segmental levels that decreased in a top–down process from head to foot (gains: 1.6 ± 0.11, 1.4 ± 0.09, and 1.1 ± 0.07 for the head, hip and knee, respectively, in the prosthesis ON condition). No significant change was observed without hearing (prosthesis OFF). During dual-tasking with the auditory memory task, the different segmental gains were reduced significantly ($p < 0.001$, $p < 0.01$, and $p < 0.05$ for the head, hip, and knee, respectively) but remained higher compared to the controls ($p < 0.001$).

DISCUSSION

POSTURE CONTROL OF THE CI PATIENTS IN STATIC CONDITIONS

In non-challenging postural conditions, with a stable support, the postural performance of the CI patients differed significantly from the healthy subjects. Their stability limits were reduced and their PII was increased, particularly in the EC condition. Postural performance remained unchanged with or without hearing and was similarly affected by dual-tasking in both groups.

These data clearly show that adults CI patients examined a long time period after CI surgery (1 year or more) have a less efficient posture control system than healthy controls. The difference in the mean age of the CI patients (59.7 years) and the controls (39.5 years) of the present study very unlikely plays a significant role. Indeed, the mean PII values (unpublished normative data) recorded with vision in 30–40 years old ($N = 90$; PII $= 0.72 \pm 0.44$) and in 50–60 years old ($N = 84$; PII $= 0.94 \pm 0.61$) healthy subjects were significantly lower than in our CI patients (PII $= 1.6 \pm 0.35$; $p < 0.001$). The differences were still significantly different without vision (PII $= 0.93 \pm 0.63$, 1.13 ± 0.58, and 2.0 ± 0.46 in the 30–40, 50–60 years old controls and CI patients, respectively). In addition, no significant differences were observed between younger and older healthy adults on the postural task performance (mean PII value and spectral power density) recorded during quiet standing (Bernard-Demanze et al., 2009).

Because of the retrospective nature of our investigation, the pre-operative vestibular function of the CI patients was not available, and in addition their hearing level was not uniforme. For the same reason, the postural tests have not been done before CI surgery, so that it was not possible to compare the

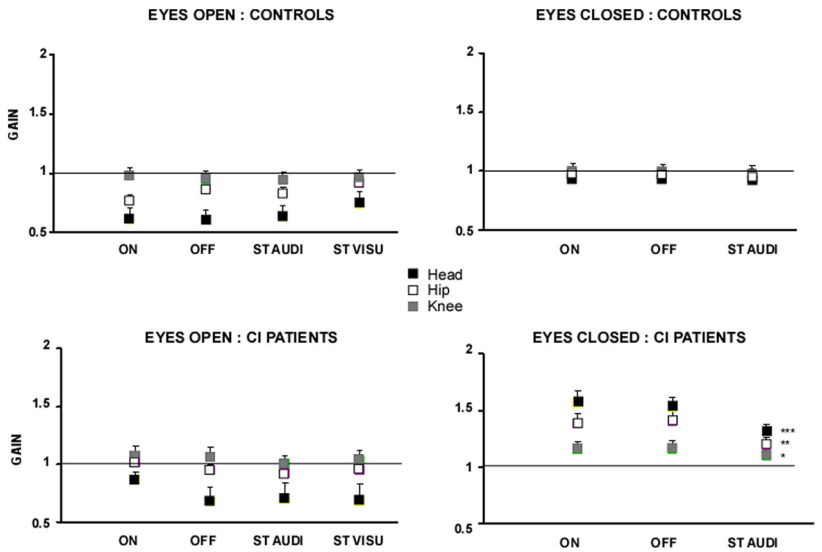


FIGURE 3 | Gain of the head, hip and knee body segments during sinusoidal platform translation at the 0.5 Hz frequency. The gains of the head (filled black squares), hip (open squares), and knee (filled gray squares) body segments, evaluated from motion analysis (Codamotion), were calculated as the ratio between platform displacement and displacement of the different body segments. Gains close to unity mean that the body segments move in phase and with the same amplitude as the platform; lower and higher gains for the head, for instance, indicate good and poor head stabilization in space, respectively. The gain values are expressed on the ordinates for each of the experimental condition tested: with (EO) or without (EC) vision, with (ON) or without (OFF) hearing, and during dual-tasking with a concomitant cognitive task consisting of a visual (visu ST) or an auditory (audi ST) memory task. Significant differences between the experimental conditions are shown by asterisks ($*p < 0.05$; $**p < 0.01$; $***p < 0.001$).

postural data before and after CI surgery. These are the main limitations of the present study. In spite of the limited number of included CI patients, significant differences compared with healthy subjects were found, however, for most of the postural tests we have performed. Our results could support previous investigations reporting delayed adverse effects of CI surgery, with occurrence of postural symptoms (Shoman et al., 2008), dizziness (Fina et al., 2003), vertigo spells (Ito, 1998; Kubo et al., 2001), and drop in the caloric response (Brey et al., 1995). Impairment of saccular/utricular function has been reported also (Basta et al., 2008). The patients' background was not controlled, as said just before, and any hypothesis on a link between CI surgery and vestibular function impairment would be purely speculative. But data from the subjective questionnaire showed they pursued normally their professional activities, and most of them had no complaints that could be related to vestibular dysfunctions: vertigo spells and instability during head motion were very uncommon complaints (3/16). And if CI vestibular damages had occurred after CI surgery, they looked like very well compensated over time. In fact, some similarities can be found between our CI patients and the compensated Menière's disease patients we have tested in a previous study (the patients had undergone a surgical vestibular neurotomy on their affected side 2–4 years before: cf. Young et al., 2012). The vestibular loss patients as well as the CI patients relied more on vision and spent more energy maintaining balance than controls. These data corroborate also a recent study showing that equilibrium function without vision was lowered in CI patients (Kluenter et al., 2010). The anxiety level could also modify the postural performance as demonstrated in both healthy and pathological subjects (Young et al., 2012). In this latter study, the Short Anxiety Screening Test (SAST) revealed that compensated Menière's patients were more anxious than healthy controls. An increased anxiety level seems another common factor to CI patients and compensated Menière's patients, since many of our CI patients reported to feel dizzy when tired or walking slowly, to have difficulties when listening music, and to be anxious when phoning with non-familiar people. In addition, the CI patients could be anxious very likely due to their poorer postural control. It should be interesting to control the anxiety level in further investigations with CI patients. Anxiety related to greater fear of fall might be involved too. Anxiety can shorten the postural reflex pathways and lead to a kind of "rigidification" (see below, the postural strategies in dynamic condition). In order to avoid a potentially dangerous situation, we found that recovered vestibular neurotomized patients (Young et al., 2012) and our investigated CI patients reduced their voluntary stability limits, and stand more rigidly.

Suppression of hearing had no effect in both populations of CI patients and controls, indicating that auditory cues do not play a significant sensory substitution role in posture recovery, contrary to the visual cues. On the other hand, the poorer postural performance of the CI patients cannot be attributed to undesirable vestibular stimulation by the prosthesis. Interestingly, dual-tasking induced similar changes of the postural performance in both groups. When a concomitant cognitive task was present, either an auditory or a visual memory task, the postural performance was improved. This confirms a previous study

we had performed in adult healthy subjects during dual-tasking (Bernard-Demanze et al., 2009). Postural performance improvement during dual-tasking can be seen as a shift of attention away from the postural task. Focusing attention on cognitive tasks delegates the postural control system to highly automatic processes, as previous reported (Huxhold et al., 2006). Following Baltes' model of task prioritization (Baltes and Baltes, 1990), we have proposed a "cognitive first principle" (Bernard-Demanze et al., 2009) for healthy younger adults during dual-tasking, that is, the mirror image of the "posture first principle" described by Shumway-Cook et al. (1997) in older subjects under dual-tasking situations. Due to the unchallenging postural context, allocating all attention resources to cognitive activity seems an optimal strategy (very likely unconscious) that does not cause resource competition and related detrimental effects. The constrained-action model (Wulf et al., 2001) that predicts interference on automatically self-organized postural behavior when attention is focused on it, has been verified: explicit instructions to focus attention on the postural task induce an increase in body sway (Vuillerme and Nafati, 2005). The CI patients used therefore the same strategy than the controls during dual-tasking, a result indicating that the cognitive functions controlling the posture control system are not modified in CI patients.

POSTURE CONTROL OF THE CI PATIENTS IN DYNAMIC CONDITIONS

In more challenging conditions, with sinusoidal for-aft displacement of the support, both groups behaved similarly when visual information was available. They showed a strategy of head stabilization in space, the so-called stable-platform strategy proposed by Horak and Nashner (1986) in healthy subjects, and reported more recently in compensated unilateral vestibular loss patients (Young et al., 2012). Dual-tasking and suppression of hearing did not modify this strategy.

By contrast, suppression of the visual input led to different effects on the postural performance, depending on the groups. While the healthy controls performance was not affected by eye closure, the CI patients relied again more on vision, and spent considerably more energy maintaining balance with the eyes closed (EC), as shown by the strongly increased spectral power density peak recorded at the 0.50 Hz stimulus frequency of platform translation. These data collected in more challenging conditions confirm the crucial role of vision described before in the CI patients under quiet standing. Prosthesis off had no significant effects on the dynamic postural performance of the CI patients, while dual-tasking reduced significantly the spectral power density peak (1.6×10^{11}) compared with the single postural task (2.7×10^{11}).

More interesting are the different strategies of posture control observed when the visual cues were suppressed. Control subjects selected a head on trunk strategy, the so-called strap-down strategy described by Horak and Nashner (1986) and characterized by a rigid whole body in space. The gain at the three segmental levels tested (head, hip, and knee) was close to unity. This "stick" behavior had already been described in adult healthy subjects under increased postural threat (Young et al., 2012), in older healthy subjects in challenging postural environments (Brown et al., 2002), and in unilateral vestibular loss patients (Young et al., 2012). The CI patients showed very poor body stabilization in space. Their head was stabilized neither in space nor on trunk. They behaved like an inverted pendulum, with the feet and knee following platform displacement (gain close to 1), and with much more high gains for the hip (gain = 1.4) and the head (gain up to 1.6). This behavior is not adapted to equilibrium maintenance, and should induce falling or stepping at higher translation frequencies. Suppression of the auditory cues did not modify this behavior. The dual-tasking condition, however, reduced the gain at the three segmental levels, suggesting again a shift of the attention resources on the cognitive task (see Lindenberger et al., 2000; Li et al., 2001), and modified posture balance, with a more rigid whole body in space.

CONCLUSION

The present study clearly shows that the CI patients' postural performance is lower compared to control subjects in both static and dynamic conditions, particularly without vision. They need visual inputs to control their posture and equilibrium in both quiet standing and more challenging postural conditions. That CI patients showed impaired postural performance and relied exclusively on a visual sensory substitution strategy are the most important results of this study. Visual sensory substitution is a common process described in functional recovery after stroke (Pérennou, 2006), Parkinson disease (Azulay et al., 2002) and vestibular pathology (Lacour, 2006). However, vicariant idiosyncratic processes are generally observed in vestibular loss patients. In a previous study performed in Menière's patients submitted to a curative unilateral vestibular neurotomy, we had described two different sensory substitution strategies, with half of the population (25 patients) relying mostly on vision and the other half (25 patients) relying mostly on somatosensory inputs (Lacour et al., 1997). In this paper, we had recommended different rehabilitation programs and exercises, depending on the sensory strategies used by the patients. In our population of CI patients, only the visual strategy was found. This shift toward a total visual dependency is very likely due to the rehabilitation procedure they were submitted to after CI surgery, that is, lip reading. And a too strong visual dependency may have deleterious effects on posture control (Bronstein, 1995). Specific rehabilitation programs should be proposed to CI patients, with exercises focusing more on proprioception and somatosensory cues.

We conclude therefore that chronic (>1 year) CI patients (1) have impaired postural performance, and (2) exhibit a sensory substitution strategy based on vision. The CI patients have to be aware of their visual dependency, particularly when they get older and have impairment of vision.

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Caloric vestibular stimulation: interaction between somatosensory system and vestibular apparatus

Gabriella Bottini[1,2]*, Martina Gandola[1], Anna Sedda[1,2] and Elisa R. Ferrè[3]

[1] *Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy*
[2] *Cognitive Neuropsychology Center, Niguarda Ca' Granda Hospital, Milan, Italy*
[3] *Institute of Cognitive Neuroscience, University College London, London, UK*
**Correspondence: g.bottini@unipv.it*

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Christophe Lopez, Centre National de la Recherche Scientifique, France

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Spatial and bodily representations are multisensory processes that imply the integration of several afferent signals into a coherent internal model of our egocentric space. Crucially, this model involves also the vestibular information from the balance organs in the inner ear (Ventre et al., 1984). Accordingly, vestibular system projections have been proven to overlap with the somatosensory system and with brain regions involved in body and space representation (Bottini et al., 1994, 1995; Fasold et al., 2002). These representations can be altered by a brain lesion and dramatically restored by physiological manipulations targeting specific sensory components, such as the caloric vestibular stimulation (CVS; see for a review Rossetti and Rode, 2002). CVS consists in a water irrigation of the external auditory canal, which induces a change in the temperature that leads to convection currents in the semicircular canals. This evokes a slow-phase nystagmus toward the stimulated ear and it elicits sensations of virtual body rotations and vertigo (Bárány, 1906; Silberpfennig, 1941; Bárány, 1967).

CVS has been used to modulate a wide range of cognitive and sensory functions in brain-damaged patients and in healthy participants (Utz et al., 2011). For instance, in right brain-damaged patients, CVS produces a temporary recovery of visuo-spatial neglect and associated symptoms, such as representational and personal neglect, anosognosia, somatoparaphrenia and motor neglect (see reviews in Rossetti and Rode, 2002; Kerkhoff and Schenk, 2012). Additionally, CVS also influences tactile perception: cold CVS delivered on the left ear transiently reduces tactile imperception (hemianesthesia) in both right and left brain-damaged patients (Vallar et al., 1990, 1993; Bottini et al., 2005). By contrast, the reversed stimulation (i.e., right ear cold CVS) is ineffective in left brain-damaged patients with the interesting exception of left brain-damaged patients with right visuo-spatial neglect (Vallar et al., 1993). More recently, similar cross-modal modulations have been described in healthy participants (Ferrè et al., 2010, 2011, 2012, 2013).

Various hypotheses have been suggested to explain the CVS-induced modulation on tactile perception. In particular, one of the most controversial issues in the classical and current literature concerns the *specificity* of these effects. Does CVS directly affect the somatosensory processing? Are the observed effects mediated by non-specific factors, such as ocular movements, spatial attention or general arousal?

Since Rubens (1985), most of the scientists believed that positive (e.g., deficits reduction) or negative (e.g., deficits worsening) effects of CVS on spatial deficits in neurological patients can be explained by low-level visuo-vestibular interactions reflecting the direction of the nystagmus (Rubens, 1985). When a leftward nystagmus is present, for instance during left-cold CVS or right-warm CVS, there is a positive effect. Conversely, with a rightward nystagmus (left-warm CVS and right-cold CVS) a deficits worsening is observed (Rubens, 1985; Vallar et al., 1990). However, this traditional explanation has been challenged by several clinical reports which highlighted an effective CVS-induced modulation on deficits that do not require visual control such as personal neglect (Cappa et al., 1987), anosognosia and somatoparaphrenia (Cappa et al., 1987; Bisiach et al., 1991; Rode et al., 1992). Similarly, the remission of hemianesthesia in blind-folded patients (Vallar et al., 1990) rules out this low-level interpretation.

Conversely, the role of non-specific effects such as spatial attention is still a matter of debate. This hypothesis argues that CVS may induce a reorientation of spatial attention toward the hemispace ipsilateral to the stimulated ear. Strong evidence against this hypothesis derives from a recent study on brain-damaged patients (Bottini et al., 2005) demonstrating that left-cold CVS also ameliorates right hemianesthesia in left brain-damaged patients (i.e., CVS at same water temperature, same stimulated ear and same leftwards slow-phase nystagmus), independently from the side of stimulation. These behavioral observations have been combined with neuroimaging data to identify the neurofunctional basis of CVS effects on touch perception in a group of normal participants and in one left brain-damaged patient. In this patient, we found that the remission of right hemianesthesia after cold-left CVS was associated with neural activity in the secondary somatosensory cortex (SII) of the undamaged hemisphere. The same region was bilaterally activated in healthy volunteers while they were touched on their right and left hand. Interestingly, the activation of SII for ipsilateral stimuli was of a greater extent in the right than in the left hemisphere in case of left tactile stimulation. These observations have been interpreted as a modulation that

did not depend on a lower-level lateral cueing effect, but rather on the activation of the hemisphere that contains a more complete representation of the tactile and body space, the right hemisphere (Bottini et al., 2005). The involvement of SII clearly indicates an overlap between tactile and vestibular projections in the human brain (case RF; Bottini et al., 1995), and it makes explanations in terms of pure spatial effects improbable.

More recent behavioral and electrophysiological studies, in healthy participants, have strengthened this suggestion. There are at least three main crucial observations ruling out interpretation in terms of non-specific attentional effects. First, left-cold CVS affects the perception of distinct somatosensory sub-modalities, i.e., touch and pain, for both the ipsilateral and contralateral hand (Ferrè et al., 2011, 2013). A simple change in the level of spatial attention would have induced a predominant effect on the hand ipsilateral to the stimulated ear. Second, CVS differentially affects touch and pain. Indeed, while CVS increased sensitivity to tactile stimuli, it reduced levels of pain (Ferrè et al., 2013). These further observations cannot be attributed merely to a spatial attention orientation effect, as in this case we would expect the same modulatory effect in both sub-modalities. Finally, CVS enhanced the N80 wave of the somatosensory-evoked potentials (SEPs) elicited by electrical stimulation of tactile afferents (Ferrè et al., 2012). Interestingly, the N80 wave is generated in the parietal operculum (Jung et al., 2009; Eickhoff et al., 2010), a region receiving strong vestibular projections. Taken together, clinical observations and psychophysical studies give support to the notion of powerful cross-modal interactions between vestibular and somatosensory systems.

Previous studies exploring more widely CVS effects also support the idea that spatial attention does not have a pivotal role. Rorden et al. (2001) did not find an effect of left-cold CVS on covert visual attention in healthy subjects. Furthermore, cold-water bilateral CVS (simultaneous stimulations of the right and left ear) was ineffective on visual neglect in brain-damaged patients, suggesting that CVS might improve neglect through a vestibular-induced specific effect (Rode et al., 2002). Moreover, it has been suggested that CVS can also modify the internal representation of the body (see for an extensive review Lopez et al., 2008). These well documented effects have been explained by the anatomical overlap and interactions of vestibular cortex and somatosensory networks subserving elementary and more structured perceptions concerning the body representation (Lopez et al., 2008, 2012).

To conclude, this evidence suggests that in healthy volunteers the effects of CVS are *specific* and related to the activation of cortico-subcortical networks (Lopez et al., 2012) involved in cross-modal interactions between somatosensory and vestibular signals. We propose that future studies are necessary to extend these findings in neurological patients to better detail the neurophysiological interaction between the somatosensory and the vestibular systems.

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Towards a concept of disorders of "higher vestibular function"

***Thomas Brandt*[1,2]*, *Michael Strupp*[1,3] *and Marianne Dieterich*[1,3,4]**

[1] German Center for Vertigo and Balance Disorders, University of Grosshadern Munich, Munich, Germany
[2] Clinical Neurosciences, University of Grosshadern Munich, Munich, Germany
[3] Department of Neurology, University of Munich, Munich, Germany
[4] Munich Cluster of Systems Neurology, SyNergy, Munich, Germany

Edited by:
Elizabeth B. Torres, Rutgers University, USA

Reviewed by:
Fred W. Mast, University of Bern, Switzerland
Stefano Ramat, Università degli Studi di Pavia, Italy

***Correspondence:**
Thomas Brandt, German Center for Vertigo and Balance Disorders, University of Munich Grosshadern, Marchioninistr. 15, 81377 Munich, Germany
e-mail: thomas.brandt@med.uni-muenchen.de

Background: Vestibular disorders are commonly characterized by a combination of perceptual, ocular motor, postural, and vegetative manifestations, which cause the symptoms of vertigo, nystagmus, ataxia, and nausea. Multisensory convergence and numerous polysynaptic pathways link the bilaterally organized central vestibular network with limbic, hippocampal, cerebellar, and non-vestibular cortex structures to mediate "higher" cognitive functions.

Anatomical classification of vestibular disorders: The traditional classification of vestibular disorders is based on the anatomical site of the lesion. While it distinguishes between the peripheral and the central vestibular systems, certain weaknesses become apparent when applied clinically. There are two reasons for this: first, peripheral and central vestibular disorders cannot always be separated by the clinical syndrome; second, a third category, namely disorders of "higher vestibular function", is missing. These disorders may be caused by peripheral as well as central vestibular lesions.

Functional classification: Here we discuss a new concept of disorders of higher vestibular function which involve cognition and more than one sensory modality. Three conditions are described that exemplify such higher disorders: room tilt illusion, spatial hemineglect, and bilateral vestibulopathy all of which present with deficits of orientation and spatial memory.

Conclusions: Further elaboration of such disorders of higher multisensory functions with respect to lesion site and symptomatology is desirable. The room tilt illusion and spatial hemineglect involve vestibular and visual function to the extent that both conditions can be classified as either disorders of higher vestibular or of higher visual functions. A possible way of separating these disorders in a first step is to determine whether the causative lesion site affects the vestibular or the visual system. For the vestibular system this lesion site may be peripheral or central. The criterion of "higher function" is fulfilled if cognition or senses other than the primarily affected one come into play.

Keywords: central vestibular disorders, vestibular cognition, higher vestibular functions, room-tilt illusion, spatial neglect

INTRODUCTION

The vestibular system is bilaterally organized: the otoliths act as sensors of gravity and linear head accelerations; the semicircular canals act as sensors of rotatory head accelerations. This input is distributed in a neuronal network that mediates perception of gravity and self-motion. The motor output of the vestibular system adjusts eyes, head, and body to an upright position in space. Vestibular pathways run from the labyrinth and the eighth nerve via the pontomedullary vestibular nuclei through ascending fibers to the ocular motor nuclei to mediate the vestibulo-ocular reflex (VOR). Once they reach the supranuclear eye-head coordination centers in the pontomesencephalic brainstem and the thalamus they are projected to several multisensory cortical areas in the temporo-parietal regions and the posterior insula for motion perception and spatial orientation. Animal studies have identified several distinct and separate areas of the temporo-parietal cortex that receive vestibular and somatosensory afferents, especially the core region of the parieto-insular vestibular cortex (PIVC; Grüsser et al., 1990a,b; Chen et al., 2011). Not only do these areas receive multisensory input, but they in turn directly project down to the vestibular nuclei (Akbarian et al., 1994). Thus, corticofugal feedback may modulate vestibular brainstem function. A homologue

of the multisensory PIVC was found to be involved in middle cerebral artery infarctions, which cause deficits in the perception of verticality and self-motion (Brandt et al., 1994). Functional imaging with MRI and PET allows us to visualize a similar cortical vestibular network in humans which shows a dominance for vestibular cortical function in the non-dominant hemisphere when activated by caloric irrigation or galvanic stimulation of the peripheral vestibular system (Dieterich et al., 2003; Dieterich and Brandt, 2008) as well as by its functional connectivity (Kahane et al., 2003; zu Eulenburg et al., 2012).

Parallel input-output loops integrate the vestibulo-cerebellar structures. The vestibular system also modulates vegetative functions via ascending and descending pathways, e.g., from the vestibular nuclei to the locus coeruleus, and the central nucleus of the amygdala (Pompeiano et al., 2002) as well as the infralimbic cortex, and hypothalamus (Balaban and Thayer, 2001; Balaban, 2004). Further, numerous polysynaptic pathways link the vestibular nuclei with hippocampal and parahippocampal structures for spatial memory and navigation via the thalamus, the dorsal tegmental nucleus, or the pedunculopontine tegmental nucleus (Smith, 1997; Horii et al., 2004). Lesions along all these pathways–from the labyrinths to the cortex–may cause vestibular disorders. Their classification will be discussed below.

PERIPHERAL OR CENTRAL VESTIBULAR DISORDERS?

The traditional classification of vestibular disorders is based on the anatomical site of the lesion and distinguishes between the peripheral vestibular system and the central vestibular system. The first includes the labyrinth and the vestibular nerve, i.e., the first- and second-order neurons. The latter involves central vestibular nuclei at the level of the pontomedullary brainstem and the pathways running from there to the vestibulo-cerebellum, brainstem, thalamus, and cortex areas (**Figure 1**). When applied clinically, this simple anatomical distinction suffers from certain weaknesses.

A CENTRAL LESION MAY MIMICK A PERIPHERAL DISORDER

The first weakness is the inaccuracy in diagnosing disorders originating at the transition from the peripheral to the central system, i.e., the root entry zone of the eighth nerve. This area is subserved by the second-order vestibular neurons traversing from the vestibular ganglion to the vestibular nucleus, and is "peripheral" by definition. Clinically, however, lesions of this fascicular region are caused by central pontomedullary brainstem disorders such as lacunar infarctions or multiple sclerosis (MS) plaques (Brandt, 1999; Kim and Lee, 2010). Thus, it is essential to differentiate peripheral vestibular neuritis from central vestibular "pseudoneuritis" already at the bedside in order to manage patients who present with signs and symptoms similar to those of acute prolonged vertigo. Whereas acute vestibular vertigo with spontaneous nystagmus and a pathological head-impulse test are typical for an acute peripheral failure, a normal head-impulse test, especially when combined with skew deviation of the eyes, indicates a central origin (Cnyrim et al., 2008; Newman-Toker et al., 2008; Kattah et al., 2009; Kim and Lee, 2012). However, it is important to note that a pathological head-impulse test can also be found in central lesions affecting the vestibular nuclei and even the cerebellum, thus mimicking a peripheral vestibular lesion (Cnyrim et al., 2008).

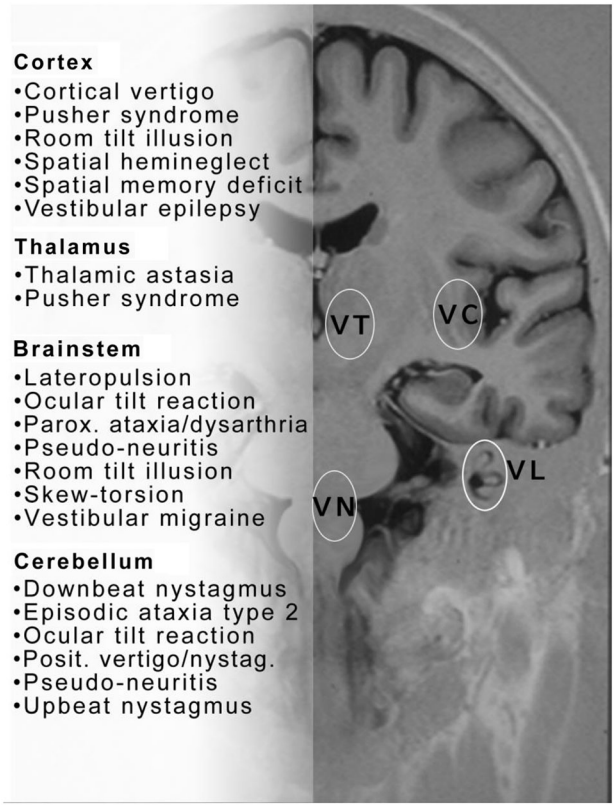


FIGURE 1 | This figure proposes a collection of clinical syndromes which may be called central vestibular disorders or disorders of higher vestibular function. They are depicted in alphabetical order and topographically grouped for cerebral cortex, thalamus, brainstem and cerebellum. The topographic assignment remains uncertain for some conditions. Note also that similar disorders occur with lesions at different sites—brainstem or cortex (room tilt illusion) or brainstem and cerebellum ocular tilt reaction (OTR)—within the central vestibular neuronal circuitry. Please note that this list does not include all central vestibular syndromes. VC = vestibular cortex; VT = vestibular thalamus; VN = vestibular nucleus; VL = vestibular labyrinth.

DIFFERENT LESION SITES ALONG VESTIBULAR PATHWAYS CAN CAUSE THE SAME SYNDROME

Peripheral disorders cause vestibular syndromes that are commonly characterized by a combination of perceptual, ocular motor, postural, and vegetative manifestations: vertigo, nystagmus, ataxia, and nausea (Brandt, 1999). Patients with central disorders may present with only single components like tilts of the perceived vertical or lateropulsion without vertigo and nystagmus. This arises if the lesion site is within the network of nuclei and pathways, which may cause ocular motor disorders in brainstem lesions or perceptual disorientation in cortical lesions.

Another weakness of a purely anatomical distinction between peripheral and central vestibular disorders involves the sensitivity

and specificity of the attribution of a specific dysfunction to a lesioned structure. Such attribution is easier to do for peripheral than for central disorders. For example, a "peripheral" canalolithiasis and cupulolithiasis of the horizontal or vertical semicircular canals can be unambiguously determined by the direction of the positioning nystagmus. In contrast, a "central" vertical divergence of the visual axes of the eyes (skew deviation) is ambiguous because it may originate in various lesion sites. Skew deviation occurs with unilateral lesions of vestibular pathways at different levels–from the vestibular nuclei to the midbrain tegmentum and the vestibulo-cerebellum (Brandt and Dieterich, 1994). Management of the thus afflicted patients, however, requires precise topographic diagnostic tools in order to identify the structures affected and the lesion's extent. They determine not only the actual neurological deficit but also allow prediction of recovery and long-term outcome. Thus, for a topographic diagnosis of vestibular brainstem and cerebellar syndromes it is necessary to seek additional neurological signs and symptoms. For example, due to the pontomedullary crossing of ascending vestibular pathways, it is helpful to identify the direction of skew deviation or the tilt of the subjective visual vertical (SVV; **Figure 2**); they indicate the side of the lesion, if the level of brainstem disorders is known or the level of the lesion, if the affected side is known (Dieterich and Brandt, 1993; Brandt and Dieterich, 1994; Zwergal et al., 2008; Baier et al., 2012).

In brief, despite some weaknesses it is logical, on the one hand, to classify peripheral and central vestibular dysfunctions according to anatomy. On the other, an additional category based on cognitive signs and symptoms is required.

HIGHER VESTIBULAR FUNCTIONS

There are additional "higher" aspects of central vestibular function and dysfunction which result from the integration of the vestibular network in cognitive functions at the cortical level and within the hippocampal and limbic system. These aspects comprise the internal representation of the body schema and the internal model of the surrounding space as well as multisensory motion perception, attention, spatial memory, and navigation. These functions can be termed "higher vestibular functions" in analogy with the well-established term "higher visual functions" in neuroophthalmology. The latter term correlates circumscribed cortical lesions with particular dysfunctions of "higher visual perception", such as recognition, memory, or spatial orientation with lesions along the ventral and dorsal streams of visual input. These streams are also called the "what" and "where" pathways (de Haan and Cowey, 2011). They seem to reflect a division of labor that is made between vision-for-action by the dorsal stream and vision-for-perception by the ventral stream (Milner and Goodale, 2008; Goodale, 2011). Accordingly, disorders of higher vestibular function are characterized by complex perceptual, sensorimotor, and behavioral deficits that exceed basic perceptions of head acceleration or motor responses, such as the vestibulo-ocular or vestibulo-spinal reflexes. The cognitive neurology of the vestibular system is being increasingly acknowledged nowadays (Seemungal, 2014). However, a description of disorders of "higher vestibular function" has not yet been elaborated, although there is experimental evidence. For example, the pusher syndrome and "visuo-spatial" hemineglect—which are not primarily considered vestibular disorders–are in some aspects related to vestibular function (Brandt, 1999; Karnath and Dieterich, 2006).

In the following we will discuss three conditions as potential candidates that will help to elaborate a classification of higher vestibular disorders, namely the room tilt illusion, spatial hemineglect, and impairment of spatial memory and navigation in bilateral vestibular loss. These three conditions will help us to elucidate the unique features of higher vestibular disorders in

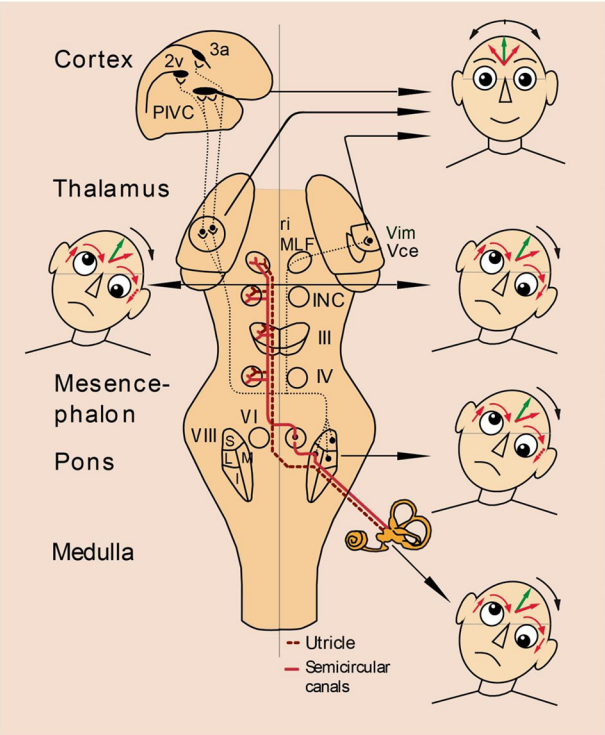


FIGURE 2 | Vestibular syndromes in the roll plane: graviceptive pathways from the otoliths and the vertical semicircular canals mediating vestibular function in the roll plane. The projections from the otoliths and the vertical semicircular canals to the ocular motor nuclei (trochlear nucleus IV, oculomotor nucleus III, abducens nucleus VI), the supranuclear centers of the interstitial nucleus of Cajal (INC), and the rostral interstitial nucleus of the MLF (riMLF) are shown. They subserve the VOR in three planes. The VOR is part of a more complex vestibular reaction, which also involves vestibulospinal connections via the medial and lateral vestibulospinal tracts for head and body posture control. Furthermore, connections to the assumed vestibular cortex (areas 2v and 3a and parieto-insular vestibular cortex, PIVC) via the vestibular nuclei and the thalamus (Vim, Vce) are depicted. Graviceptive vestibular pathways for the roll plane cross at the pontine level. The ocular tilt reaction (OTR; with skew torsion, head tilt, and tilt of perceived vertical) is depicted schematically in relation to the level of the lesion: ipsiversive OTR with peripheral and pontomedullary lesions (bottom two of the heads on the right); contraversive OTR with pontomesencephalic lesions (head on the left). In cases of lesions of the vestibulothalamic tract isolated tilts of SVV may be ipsiversive and in vestibular thalamic lesions, the tilts of SVV may be contraversive or ipsiversive; in vestibular cortex lesions, they are preferably contraversive (top two of the heads on the right). OTR is not induced by supratentorial lesions above the level of INC.

contrast to those of higher disorders of other senses like vision or hearing. In the process the difficulties and limitations of such attempts to nosologically separate these disorders from other sensory modalities and even from peripheral vestibular disorders will also become overt.

DISORDERS OF HIGHER VESTIBULAR FUNCTION VERSUS DISORDERS OF HIGHER VISUAL FUNCTION

There are similarities and differences between the higher sensory disorders of visual and vestibular function. They are similar in that both manifest with cognitive disturbances of spatial orientation, attention, spatial memory, and navigation. They are typically different in the following ways:

- In higher visual disorders the lesion site is mostly within the visual cortex, and the symptomatology arises from a dysfunction of the visual cortex. However, the hierarchically organized cortical visual network is much more complex and larger than that of the vestibular cortex.
- In higher vestibular disorders the lesion site may involve the vestibular cortex, but it may also be located in the subcortical vestibular circuitry or even in the peripheral end-organs.
- Higher vestibular disorders often involve dysfunction of other sensory modalities so that the same disorder can be called a higher vestibular, higher visual, or higher somatosensory disorder.
- Some higher vestibular dysfunctions are only the cognitive symptoms caused by a peripheral vestibular disorder.

All of the above listed features are best illustrated by the rare vestibular syndrome of room tilt illusion.

ROOM TILT ILLUSION

Transient upside-down inversion of vision—the room tilt illusion—has been repeatedly described in patients with lower brainstem infarctions (Ropper, 1983; Tiliket et al., 1996; Sierra-Hidalgo et al., 2012) or with cortical lesions (Solms et al., 1988), especially in cases of vestibular epilepsy (Smith, 1960). These illusions last for seconds or minutes, rarely up to hours. They are often associated at the beginning with rotational vertigo, and recovery is either rapid or involves a gradual uprighting to normal position. Transient upside-down vision or 90° tilts are obviously vestibular signs that indicate a misperception of verticality. Spatial orientation of verticality is based on the interactions between the visual and vestibular systems. Both senses provide us with cues about vertical orientation in 3-D coordinates. The visual and vestibular cortices have to match vestibular spatial coordinates in three dimensions with the orientation of the visual scene to determine the unique egocentric perception of right and left, up and down, and fore and aft. It is not possible to perceive two different verticals, a visual and a vestibular one, at the same time. In brief, room-tilt illusions are, in our opinion, transient mismatches of the visual and vestibular 3-D map coordinates that occur in 90° or 180° steps (Brandt, 1997). They are the erroneous result of an attempted cortical match (**Figure 3**).

This condition corresponds with several of the above-described typical features that distinguish higher vestibular from higher visual disorders. First, the lesion site is mostly subcortical, i.e., within the brainstem or the peripheral end-organ (e.g., Meniere's disease, bilateral vestibular failure). Second, the cause of the disease is vestibular; the symptomatology, however, is visual. Third, the clinical syndrome of room tilt illusion could be classified as either a higher vestibular or a higher visual disorder.

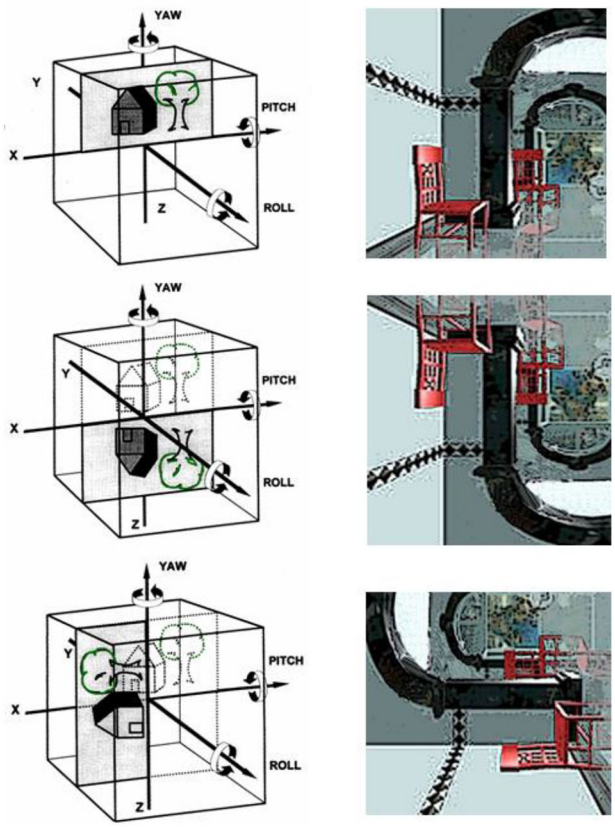


FIGURE 3 | Room-tilt illusion: schematic representation of the head as a cube with the cortical matching of the vestibular and the visual 3-D coordinate maps. The three major planes of action of the vestibular system are the frontal roll, the horizontal yaw, and the sagittal pitch about the *x*, *y* and *z* axes, respectively. (Top) Visual scene matches with the vestibular coordinates; (middle) room tilt illusion with 180° tilted visual scene in the pitch plane (upside-down vision); (bottom): room tilt illusion with 90° tilt in the roll plane (modified from Brandt, 1997).

SPATIAL NEGLECT

We hypothesize that the mechanisms of visuo-spatial neglect are predominantly elicited by a vestibular tonus imbalance (Brandt, 1999; Karnath and Dieterich, 2006; Brandt et al., 2012). Spatial neglect is a disorder of spatial attention and orientation; awareness of visual stimuli is disrupted and occurs in one egocentric hemifield that is contralateral to an acute temporo-parietal lesion of the (most often) right hemisphere (Vallar and Perani, 1986). Patients so afflicted may have preserved visual fields, but they spontaneously direct their spatial attention and eye and head movements to the ipsilesional hemifield. This results in a visuospatial neglect of stimuli in the contralateral hemifield. Karnath and Rorden (2012) stress the "heterogeneous collection

of symptoms with controversial anatomical correlates". They also draw attention to biased gaze deviation and search, mainly due to lesions of the right hemisphere perisylvian region, and object-centered deficits (line bisection), caused primarily by more posterior and inferior lesions.

Imaging techniques in patients with neglect provided evidence that the cortical areas involved are the superior temporal cortex, the insula, the temporo-parietal junction (Karnath and Dieterich, 2006), and the middle frontal gyrus and the posterior intraparietal sulcus (Ptak and Schnider, 2011). Some of these structures are core regions of the cortical multisensory vestibular network (Brandt and Dieterich, 1999; zu Eulenburg et al., 2012). It has been found that the dominance for vestibular cortical function lies in the nondominant hemisphere, i.e., the right hemisphere in right-handers (Dieterich et al., 2003). Studies showing that vestibular (caloric) stimulation significantly improved spatial functioning have demonstrated the important role of the vestibular system in neglect (Cappa et al., 1987; Vallar et al., 1993). For example, when vestibular stimulation was combined with neck muscle vibration, the horizontal deviation combined linearly, adding or neutralizing the effects observed during application of both types of stimulation (Karnath, 1994). Therefore, the question arose as to whether spatial neglect is a disorder of the "multisensory vestibular cortex" (Brandt, 1999; Karnath and Dieterich, 2006). In **Figure 4** a schematic drawing depicts the major anatomical structures involved and their functional connections as the basis for a hypothetical model of certain underlying mechanisms (Brandt et al., 2012).

This condition is also in line with several of the above-described features. First, the lesion site is in the vestibular cortex of the right hemisphere, which is the dominant hemisphere for the vestibular system in right-handers. However, neighboring non-vestibular structures of the temporo-parietal cortex and the thalamus are also involved, i.e., a lesion restricted to the vestibular cortex does not cause hemineglect. Second, the symptomatology involves visual and somatosensory perception as well as ocular motor exploration and eye-hand coordination. Third, the clinical syndrome could be equally classified as a higher vestibular, a higher visual, or a higher somatosensory disorder.

BILATERAL VESTIBULAR LOSS WITH SPATIAL MEMORY DEFICIT

Key symptoms of bilateral vestibulopathy are (i) movement-dependent postural dizziness and unsteadiness of gait and stance (exacerbated in the dark and on unlevel ground); they are absent when sitting or lying; (ii) blurred vision when walking and during head movements (oscillopsia); and (iii) impaired spatial memory and navigation (Brandt et al., 2013). Patients mostly complain about postural vertigo and gait unsteadiness when moving. They are typically free of symptoms under static conditions, i.e., when sitting or lying. About 40% of those affected notice illusory movements of the surroundings (oscillopsia) while walking or running, and consequently can no longer read street signs or definitely identify the faces of people approaching them.

An intact vestibular function is important for spatial orientation, spatial memory, and navigation (Smith, 1997). Patients with bilateral vestibulopathy have significant deficits of spatial memory and navigation (tested with a virtual variant of the Morris water task) as well as atrophy of the hippocampus (Brandt et al., 2005), but the rest of their memory functions are not affected. The latter was tested by the Wechsler Memory Scale-Revised in full which constitutes the most universally employed memory test battery (Brandt et al., 2005). Patients with unilateral labyrinthine failure, however, do not have significant disorders of spatial memory or atrophy of the hippocampus (Hüfner et al., 2007). Spatial navigation requires a continuous representation of the location and motion of the individual within a 3-D environment, whose coordinates are provided mainly by vestibular and visual cues. Consequently hippocampal atrophy may impair complex forms of spatial memory processing, while non-spatial functions remain well preserved. Perhaps the ancient phylogenetic role of the hippocampus in spatial memory processing (Kessels et al., 2004), which requires an intact vestibular input, is more sensitive to hippocampal atrophy than more advanced, non-spatial roles that rely additionally on the surrounding medial-temporal lobe and prefrontal tissue (Markowitsch et al., 2003).

This disorder especially reflects the last of the four features that distinguish higher vestibular from higher visual disorders. Bilateral vestibular loss is a well-defined peripheral disorder of both labyrinths or vestibular nerves. Impaired spatial memory, orientation, and navigation are additional higher vestibular symptoms, i.e., cognitive consequences of the absent vestibular input.

CONCLUSIONS

The three above-described syndromes represent cognitive disorders of higher vestibular function, a clinically desired third category of vestibular disorders in addition to the traditional distinction between peripheral and central vestibular disorders. They involve not only convergence of multisensory input but also of sensorimotor integration with spatial memory, orientation, attention, navigation, and the interaction of body and surround during locomotion. Other examples are vestibular epilepsy, the pusher syndrome, thalamic astasia, or lateropulsion with tilts of perceived verticality. Some may manifest as paroxysms or transient episodes such as vestibular epilepsy and room tilt illusion. Some resolve spontaneously or within days to weeks with the support of physical therapy, as in pushing behavior. Sometimes patients recover but have residual deficits such as extinction in visuospatial hemineglect. The causative lesion is not necessarily restricted to cortical structures; an example of this is the room tilt illusion, which may be elicited by peripheral or central vestibular dysfunctions originating from the labyrinth to the vestibular cortex. Disorders of higher vestibular function can manifest as a consequence of a peripheral vestibular failure, e.g., deficits in orientation, spatial memory, and navigation in bilateral vestibular loss.

An elaboration of a classification of disorders of higher vestibular function has to consider multisensory convergence, which for the vestibular system—in contrast to the visual or auditory systems–already occurs at the level of the vestibular nuclei. The vestibular cortex is not a "primary sensory cortex" like the visual cortex. All vestibular cortex neurons are multisensory and respond to stimuli of various modalities. Disorders of higher vestibular or higher visual function could be separated by the

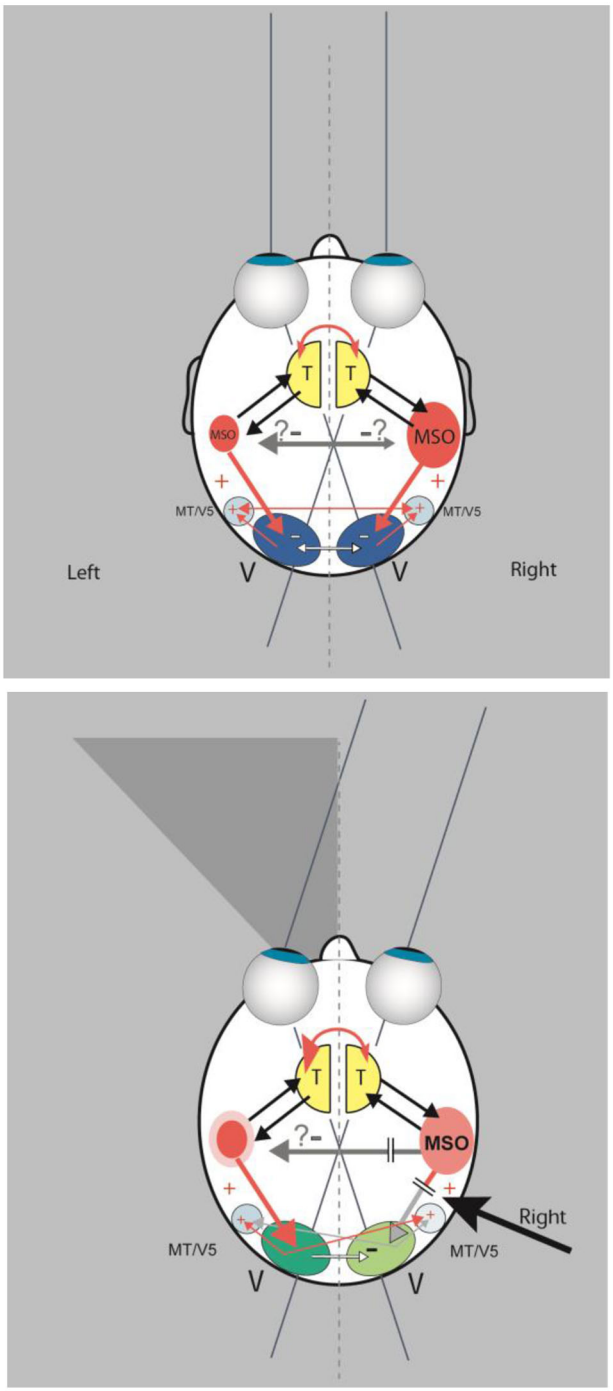


FIGURE 4 | (Top) In this scheme a double organization of the spatial attention and orientation center, represented by an "MSO" (multisensory orientation) in each hemisphere, is assumed, as is a dominance of the right hemisphere. Interhemispheric transcallosal connections are inhibitory. The MSO receives vestibular and somatosensory input from the thalamus (T) and directs visual attention by excitatory connections to the ipsilateral or contralateral visual cortex (V). The schematic drawing shows also transcallosal connections between the visual cortices. They are mainly inhibitory (white arrows) and to a lesser extent excitatory (thin red arrows) for bilateral activation of the motion-sensitive areas MT/V5. **(Bottom)** A lesion of the dominant MSO in the right hemisphere causes a left-sided visuo-spatial neglect due to less excitation ("deactivation") of the ipsilateral visual cortex. This is further suppressed by increased inhibition from the contralateral visual cortex. While the motion-sensitive area MT/V5 receives less input from the ipsilateral visual cortex, it still receives excitatory input from the contralesional MT/V5. Modulation of the left visual cortex could hypothetically result in enhanced visuo-spatial attention within the right hemifield due to the increased activation from the nondominant MSO and less inhibition from the ipsilateral right visual cortex (modified from Brandt et al., 2012).

lesion site by determining whether it affects the vestibular or the visual system. Such a distinction is, however, clinically unsatisfying, especially when the symptomatology is dominated by a dysfunction of another sensory modality. This is the case for the room tilt illusion in which the lesion site is in the vestibular system, but the symptomatology of an upside-down inversion of vision is in the visual system. Thus, some conditions can be classified as either higher vestibular or higher visual dysfunction depending on the classifying criterion, which can be the site of the lesion or the symptomatology. A comprehensive elaboration of disorders of all higher sensory functions is still necessary.

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The neural encoding of self-generated and externally applied movement: implications for the perception of self-motion and spatial memory

Kathleen E. Cullen*

Aerospace Medical Research Unit, Department of Physiology, McGill University, Montreal, QC, Canada

Edited by:
Paul Smith, University of Otago Medical School, New Zealand

Reviewed by:
Patrizia Fattori, University of Bologna, Italy
Dennis Eckmeier, Cold Spring Harbor Laboratory, USA
Alan M. Brichta, The University of Newcastle, Australia

***Correspondence:**
Kathleen E. Cullen, Aerospace Medical Research Unit, Department of Physiology, McGill University, McIntyre Medical Building, Room 1219A, 3655 Promenade Sir William Osler, Montreal, QC H3G 1Y6, Canada
e-mail: kathleen.cullen@mcgill.ca

The vestibular system is vital for maintaining an accurate representation of self-motion. As one moves (or is moved) toward a new place in the environment, signals from the vestibular sensors are relayed to higher-order centers. It is generally assumed the vestibular system provides a veridical representation of head motion to these centers for the perception of self-motion and spatial memory. In support of this idea, evidence from lesion studies suggests that vestibular inputs are required for the directional tuning of head direction cells in the limbic system as well as neurons in areas of multimodal association cortex. However, recent investigations in monkeys and mice challenge the notion that early vestibular pathways encode an absolute representation of head motion. Instead, processing at the first central stage is inherently multimodal. This minireview highlights recent progress that has been made towards understanding how the brain processes and interprets self-motion signals encoded by the vestibular otoliths and semicircular canals during everyday life. The following interrelated questions are considered. What information is available to the higher-order centers that contribute to self-motion perception? How do we distinguish between our own self-generated movements and those of the external world? And lastly, what are the implications of differences in the processing of these active vs. passive movements for spatial memory?

Keywords: proprioception, self-motion, head direction cells, place cells, sensory coding, efference copy, corollary discharge, voluntary movement

FUNCTIONALLY ANALOGOUS CELLS TYPES IN THE VESTIBULAR PATHWAYS OF MONKEY AND MOUSE

The vestibular system provides the brain with information about the motion of the head relative to space and is comprised of two types of sensors: the three semicircular canals, which sense angular rotation in three dimensions and the two otolith organs (the saccule and utricle), which sense linear motion (i.e., gravity and three dimensional translational movement). In turn, the receptor cells of the semicircular canals and otoliths send signals through the vestibular nerve fibers to the vestibular nuclei (VN).

To date, the coding of vestibular information at the level of single vestibular nerve afferents and their target neurons in the VN has been well characterized in alert behaving monkeys. Notably, neurons predominantly encode rotational head velocity and linear head acceleration. Vestibular afferents can be further characterized on the basis of their baseline discharge regularity as regular or irregular (reviewed in Goldberg, 2000; Cullen, 2011). In addition, their target neurons in the VN can be divided into three primary groups on the basis of their sensitivities to applied head motion and eye movements (Cullen and McCrea, 1993; Cullen et al., 1993, and reviewed in Cullen, 2012). Two classes of neurons—each with a specific combination of eye movement and vestibular related responses—are thought to provide the substrate for the generation and adaptation of the vestibulo-ocular reflex. In particular, eye movement related inputs from oculomotor areas of the brainstem (e.g., the nucleus prepositus and reticular formation), the accessory optic system, and the vestibular cerebellum (flocculus and ventral paraflocculus) provide saccade, pursuit and optokinetic–related inputs to both neuron classes. These extravestibular inputs contribute to the control and modulation of both visually-driven eye movements and the vestibulo-ocular reflex. In contrast, a third subgroup of neurons that responds to vestibular stimulation but not eye movements projects both to: (i) the spinal cord and (ii) upstream centers including the thalamus and vestibular cerebellum (reviewed in Cullen, 2012), to ensure the maintenance of posture and accurate perception of self-motion.

More recently, a corresponding series of studies in mice examined the coding of vestibular information at the level of single vestibular nerve afferents and VN neurons. Comparison with findings in monkey reveals that mouse vestibular afferents can likewise be classified on the basis of their discharge regularity, but they are on average 3–4 times less sensitive to head velocity (**Figure 1A**; Yang and Hullar, 2007; Lasker et al., 2008). Similarly, mouse VN neurons (Beraneck and Cullen, 2007) display relatively

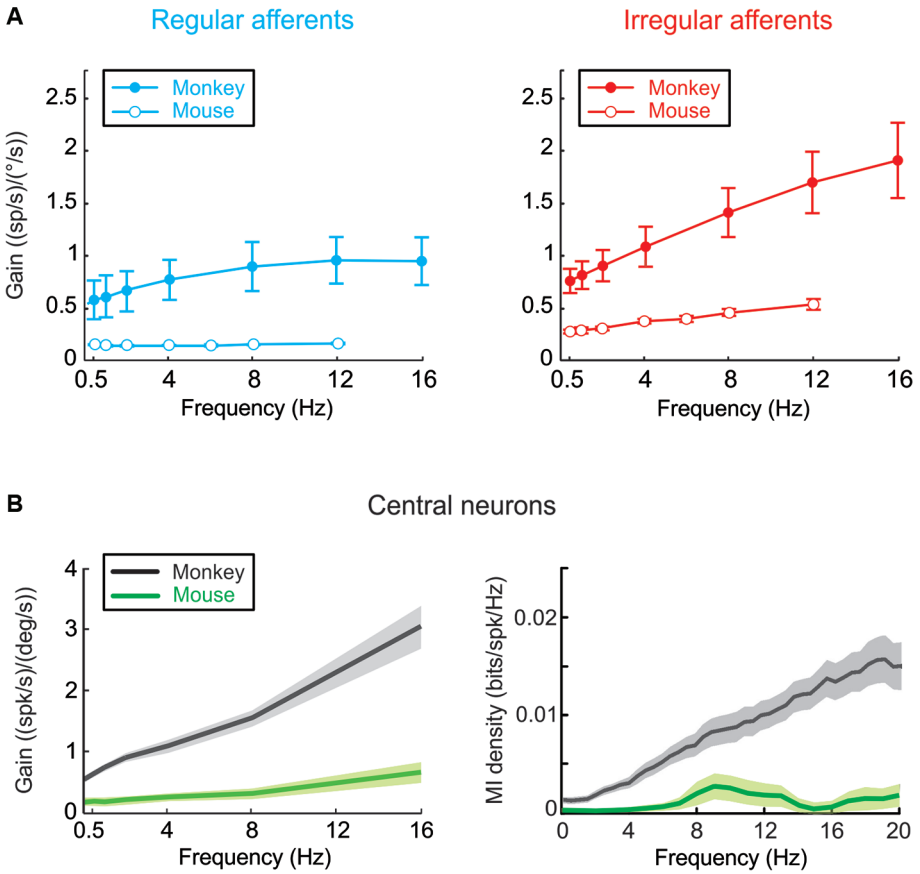


FIGURE 1 | (A) Mouse vestibular afferents can be classified on the basis of their discharge regularity, and are on average 3–4 times less sensitive to head velocity when compared to monkey afferents. **(B)** Comparison of rotational sensitivities and mutual information density of mouse and monkey VN neurons. (Monkey data are adapted from Massot et al., 2011, 2012).

low sensitivities to vestibular stimulation as compared to neurons in monkeys (Massot et al., 2011, 2012). Furthermore, simultaneous recordings of eye and head motion responses revealed subgroups comprising both eye motion sensitive and insensitive neurons in the mouse VN similar to those reported in monkey (Beraneck and Cullen, 2007).

Why is early vestibular processing in mice characterized by lower pathway modulation than in monkeys? The general decrease in modulation could potentially indicate sensory processing has adapted to account for differences in the stimuli experienced by each species in its natural environment. Alternatively, it is also possible that neuronal sensitivities are matched to the specific constraints of the reflexes that the mouse sensory-motor pathways evolved to control. If mice have a more limited need for perceptual and behavioral accuracy, then the relatively lower discharges of their early vestibular pathways could correspond to reduced information transmission (Vinje and Gallant, 2000; Borst and Haag, 2001). This proposal is consistent with our preliminary results that in mice eye-movement insensitive neurons encode substantially less information than do monkey VN neurons (**Figure 1B**; Jamali et al., 2010; Massot et al., 2011). Taken together, current evidence suggests that evolutionary pressure adjusts characteristics of sensory transmission in early vestibular processing to meet certain functional requirements, which differ across species (see also, Niven et al., 2007).

WHAT INFORMATION IS AVAILABLE TO HIGHER-ORDER CENTERS THAT CONTRIBUTE TO THE PERCEPTION OF SELF-MOTION?

As noted above, vestibular afferents exclusively encode head motion information and project to a class of neurons in the VN that in turn project to both the spinal cord and upstream centers to ensure the maintenance of posture and perception of self-motion. In mice the majority of these VN neurons are sensitive to the dynamic stimulation of neck proprioceptors (Medrea and Cullen, 2013). This finding is consistent with reports that both vestibular and proprioceptive sensory inputs can modulate the response of VN neurons in alert squirrel monkeys (Gdowski and McCrea, 2000) and cynomolgus monkeys (i.e., *Macaca fascicularis*; Sadeghi et al., 2009). In contrast, in alert rhesus monkeys (*Macaca mulatta*), we found that VN neurons do not normally respond to passive stimulation of neck proprioceptors (Roy and Cullen, 2001, 2002, 2003). Instead, such integration is observed only at the next stage in the cerebellum (Brooks and Cullen, 2009,

2013). Interestingly, however, after peripheral vestibular loss, VN neurons in the rhesus monkeys respond to passive proprioceptive stimulation indicating that sensory substitution occurs at the earliest stages of vestibular processing to mediate compensation (Sadeghi et al., 2010, 2011, 2012).

In mice, proprioceptive-related responses can be either "additive" or "subtractive" to vestibular sensitivities. Put another way, they can function to either enhance or reduce vestibular-related modulation when the head is moved relative the animal's body. This is a condition in which both self-motion sensory cues are present—the vestibular sensors are stimulated by the movement of the head relative to space, while neck proprioceptors are simultaneously activated by the resultant stretch applied the neck. Notably, in mice a given neuron's response to such combined stimulation can be well predicted by the simple linear sum of its response to each stimulus when applied alone, consistent with previous studies in alert squirrel and cynomolgus monkeys (Gdowski et al., 2001; Sadeghi et al., 2009).

Neck sensitive VN neurons also encode a static neck position signal in alert mice (Medrea and Cullen, 2013) as well as in rats (e.g., Barresi et al., 2013) but not in primates. As detailed below, this static signal of proprioceptive origin is observed during both active and passive self-motion. Thus, this input is of particular interest since it can potentially provide an important heading signal to upstream structures for the computation of spatial orientation.

The lack of a static head position signal in primates as compared to rodents may reflect differences in the active control of gaze as well as habitat. Monkeys, are frontal-eyed animals with a retina specialized for high-acuity vision (fovea). In particular, monkeys often use voluntary coordinated eye-head and eye-head-body gaze shifts (McCluskey and Cullen, 2007) to precisely align gaze when exploring their environment, whereas mice are afoveates for which head and body motion are typically more closely linked during exploration (see Stahl et al., 2006). It is thus likely that the static neck sensitivity coded by mouse VN neurons plays a vital role in stabilization of the head relative to the body during exploration via the vestibulo-collic reflex (e.g., Baker, 2005; Takemura and King, 2005). In contrast, such default stabilization would be potentially detrimental in monkeys, since it would be counterproductive to the voluntary head movements that are frequently made by this species.

HOW DO WE DISTINGUISH BETWEEN OUR OWN SELF-GENERATED MOVEMENTS AND THOSE OF THE EXTERNAL WORLD?

Voluntary neck movements generate egocentric motor-related as well as proprioceptive signals. In the murine vestibular nucleus, these signals are combined with allocentric vestibular signals (head motion in space) at the neuronal level. Specifically, the simple linear summation of a neuron's sensitivities to passive vestibular and neck proprioceptive stimulation applied alone no longer predicts VN neurons responses (Medrea and Cullen, 2013). Instead, neuronal responses are suppressed for self-generated head motion in a manner similar to what has been observed in monkey (Gdowski and McCrea, 2000; Roy and Cullen, 2001; Sadeghi et al., 2009). Evidence from experiments in monkeys suggest that a neural copy of the motor command that initiates the active motion, is used to cancel self-generated sensory input during active head movements (e.g., Roy and Cullen, 2004; Sadeghi et al., 2009). A comparable mechanism may underlie the analogous suppression of self-produced vestibular stimulation observed in the VN of mice.

It is notable, that a series of lesion and inactivation studies has provided evidence that vestibular inputs are essential to ensure the tuning of the head-direction cell network. Head direction cells are thought to integrate signals of vestibular origin to maintain a signal of cumulative rotation (reviewed in Taube, 2007) and are found in many brain areas, including the postsubiculum, retrosplenial cortex, thalamus, lateral mammillary nucleus, dorsal tegmental nucleus, striatum and entorhinal cortex. A characteristic of head direction cells is that they selectively fire when animal's head points in a specific direction. Based on anatomical studies, it has been further suggested that three nuclei could relay vestibular signals to the head-direction pathway including: the nucleus prepositus, the supragenual nucleus, and the paragigantocellular nucleus (reviewed in Shinder and Taube, 2011). However, at least in monkeys, the nucleus prepositus predominantly encodes eye-movement information during both externally applied and passively generated motion (Dale and Cullen, 2013). On the other hand, lesions to the supragenual nucleus can destabilize head-direction cell tuning in rats (Clark and Taube, 2012). Future neurophysiological experiments in mice and rats quantifying both vestibular and extravestibular related responses during self-motion will be needed to fully understand the nature of the signals that these nuclei relay to upstream structures.

WHAT ARE THE IMPLICATIONS REGARDING THE NEURAL ENCODING OF SELF-GENERATED VS. EXTERNALLY APPLIED MOTION FOR SPATIAL MEMORY?

What is the functional significance of the differential encoding of active and passive motion by early vestibular pathways in mice? Three important implications are outlined below (**Figure 2**).

First, the descending projections of this specific class of VN neurons mediate spinal postural reflexes such as the vestibulo-collic reflex (Wilson et al., 1990; Boyle et al., 1996). Thus, the fact that sensory inputs produced by volitional movement are suppressed suggests that these stabilizing reflex pathways are themselves suppressed. This is helpful, since an intact reflex command would be counterproductive to the intended movements when the behavioral goal is to generate active self-motion.

Second, the multimodal information encoded by the ascending thalamocortical projections of this specific class of VN neurons make a major contribution to higher-level functions including the computation for spatial orientation and memory. Two facts discussed above play together. On the one hand multimodal integration in the VN is more comprehensive in mice than in monkeys. On the other hand, we found that monkeys might implement some functionality found in the murine VN in the cerebellar cortex instead (Brooks and Cullen, 2009, 2013).

Third and finally, recent neurophysiological findings have specific implications for the head direction cell network. While this

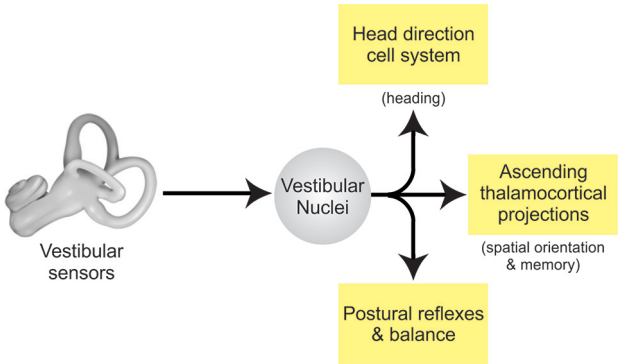


FIGURE 2 | Vestibular pathways for spatial memory. Vestibular signals from the labyrinth of the inner ear are transferred to the VN via the vestibular afferents of the VIII nerve. In turn, the VN projects to other brain areas to: (i) control posture and balance, (ii) produce estimates of spatial orientation, and (iii) encode heading direction.

network is commonly thought to integrate signals of vestibular origin to maintain a signal of cumulative rotation (reviewed in Taube, 2007), the neurophysiological studies reviewed above have established that the coding of vestibular information at the first central stage of processing is determined by on-going behavior in both primates and rodents. In particular, vestibular information is combined with egocentric information including proprioceptive and motor-related signals at this initial stage of sensory processing. One possibility is that egocentric cues provided by the proprioceptive and motor-related signals in early vestibular processing also make important contributions to the head direction cell network activity (Wiener et al., 2002; Taube and Basset, 2003). Notably, the observed motor-related responses could potentially provide a directional heading signal with anticipatory features. Furthermore, it is likely that different species employ characteristic integration strategies, based on specific weighting of egocentric as well as allocentric cues, to compute the head direction signal. For instance, Yoder and Taube (2009) reported that rat head direction cells are more influenced by external (i.e., visual) cues than those of mice. Future work is needed to fully understand the contribution of the egocentric signals encoded by vestibular pathways to head direction cell signal generation and whether there are important differences in this computation across species (e.g., mouse vs. rat vs. monkey). This knowledge will be essential in furthering our understanding of how input pathways such as the early vestibular system that encode both allocentric and egocentric information, contribute to the neural representation of direction encoded by higher level structures.

CONCLUSION

It is generally assumed the vestibular system provides a veridical representation of head motion to higher order centers for the perception of self-motion and spatial orientation. However, as reviewed above, the findings of recent electrophysiological studies in monkeys and mice have challenged this assumption. Instead, under natural conditions, behavioral context governs how vestibular information is encoded at the first central stage of vestibular processing. Not only is processing inherently multimodal, but the manner in which multiple inputs are combined is adjusted to meet the needs of the current behavioral goal. Notably, in natural conditions, neurons in the VN can distinguish between active and passive motion—responding far more robustly to passive movements. These results have important implications for understanding the computations that underlie the spatial orientation signals encoded by neurons in the head direction cell network and areas of multimodal association cortex that underlie self-motion perception and spatial memory.

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Toward a vestibular contribution to social cognition

Diane Deroualle and Christophe Lopez*

Laboratoire de Neurosciences Intégratives et Adaptatives, UMR 7260, Centre Saint Charles, Fédération de Recherche 3C, Centre National de la Recherche Scientifique, Aix-Marseille Université, Marseille, France
**Correspondence: christophe.lopez@univ-amu.fr*

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Pierre Denise, Université de Caen Basse-Normandie, France

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Social cognition encompasses perception of self and others as well as self-other interactions. Self-other interactions rely on a wide range of cognitive processes such as memory, language, reasoning, and emotion processing (Beer and Ochsner, 2006). Within the last few years, one productive line of research in social neuroscience has investigated the multisensory and motor foundations of self-other interactions, including emotion perception, emotional contagion, empathy, self-other distinction, or self-other knowledge (e.g., Singer et al., 2004; Iacoboni et al., 2005; Ambrosini et al., 2013; Manera et al., 2013). While a strong emphasis has been traditionally put on visual processes, recent research has noted that self-other distinction and mirroring also require processing of auditory (e.g., self-other voice recognition), proprioceptive, and interoceptive signals (Damasio, 2000; Schutz-Bosbach et al., 2006; Tsakiris et al., 2011; Seth, 2013; Xu et al., 2013). In spite of this multisensory development, a vestibular contribution to the embodied mechanisms of social interactions has until now been largely overlooked. This is surprising as the vestibular system has been involved in a growing number of cognitive functions (Smith et al., 2005; Miller and Ngo, 2007; Gurvich et al., 2013), in addition to its crucial role in distinguishing self- and non-self motion. The claim of the present opinion article is that vestibular information should not be ignored when investigating the sensorimotor foundations of social cognition. We present several lines of evidence indicating that vestibular signals may be involved in the sensory bases of self-other distinction and mirroring, emotion perception and perspective taking.

DISTINGUISHING SELF AND NON-SELF

One characteristic of the vestibular system is to code *absolute* body motion in space (Berthoz, 2000). The vestibular system contains "inertial sensors" (i.e., types of accelerometers and gyroscopes) activated by gravito-inertial forces generated by self-motion. As a consequence, vestibular sensors function without external references (besides Earth's gravity), i.e., without allocentric or egocentric references, in contrast with the visual and somatosensory coding of motion. Vestibular signals should be a crucial component of self-other distinction by discriminating between "*I*" (the subject of experience) have moved (or "*I*" have been moved), *another person* has moved, or the *environment* has moved. As a consequence of this, we propose that vestibular signals should be important to construct a sense of agency (the sense of being the agent of actions) and ownership of actions ("this action was *mine*"), two major constituents of self-consciousness (Jeannerod, 2006). Clinical observations revealed that vestibular signals are important to distinguish between self- and non-self motion, as patients with a vestibular loss are more likely to incorrectly interpret motion of objects or their environment as self-motion (e.g., Johnson et al., 1999). In addition, these patients may report not being in control of their self, as measured using depersonalization and derealization questionnaires (Yen Pik Sang et al., 2006).

In addition to distinguishing self- and non-self motion, we propose that vestibular signals are also important for constructing a more global sense of body ownership ("this body is *mine*"). Observations in neurological patients with somatoparaphrenia—who misattribute their own hand as belonging to someone else—are striking examples of relations between vestibular processing and body ownership. Caloric vestibular stimulation was showed to temporarily suppress somatoparaphrenia in these patients (Bisiach et al., 1991; Rode et al., 1992). In addition, experiments using the "rubber hand illusion" showed that galvanic vestibular stimulation increased illusory attribution of a non-corporeal hand under appropriate visuo-tactile conflicts (Lopez et al., 2010). Conclusively, these observations indicate that vestibular stimulation can interfere with the sensory and neural mechanisms of body ownership (see below) and modify the definition of self-other boundaries.

VISUAL-VESTIBULAR INTERACTIONS FOR THE PERCEPTION OF BODIES AND EMOTIONS

Humans have evolved under a constant gravitational field. This invariant in the environment has strongly constrained the way bodies move and has moulded the development of the human sensorimotor system (Berthoz, 2000). Several studies have suggested the existence of an internal model of gravity in the human brain and highlighted the crucial role of the vestibular system in sensing gravity and constructing such model (McIntyre et al., 2001; Indovina et al., 2005). Interestingly, interpreting other's emotions and intentions requires subtle detection of other's body configurations (including facial expressions) and movements, a function for which the human visual system is finely tuned (Puce and Perrett, 2003; Troje et al., 2005). This knowledge appears fundamental for the survival of species as basic interactions necessitate detecting whether others have threatening posture and motion or aversive facial expressions. Several studies suggest that perception of faces and bodies depends on low-level visual mechanisms that are strongly orientation-dependent, i.e., depends on the visual stimuli orientation with respect to the observer's body and gravity. For example, Lobmaier and

Mast (2007) showed that face perception depends on its orientation with respect to gravity. Lopez et al. (2009) showed that how we interpret the stability of whole-body postures is also a function of the gravitational reference. These data suggest that vestibular otolithic signals (sensing gravity) are used for the visual interpretation of socially relevant human body postures and kinematics and contribute to predict other's emotions and intentions.

THIRD-PERSON PERSPECTIVE TAKING AND EMPATHY

Another important aspect of social interaction is our ability to take another person's point of view—in other words, our ability to put oneself in someone else's shoes. This ability is referred to as "third-person perspective taking" in the literature and can be seen as the visuo-spatial ability through which one temporarily simulates the visual perspective of another individual (Vogeley and Fink, 2003). This is used, for example, to decide whether an object is on the right or left of someone (David et al., 2006; Lambrey et al., 2012). Psychophysical investigations have revealed that third-person perspective taking is rapid and involuntary (Tversky and Hard, 2009; Samson et al., 2010) and can be used to understand and predict feelings and intentions of others (Zwickel and Müller, 2010). Thus, some authors have drawn parallels between visuo-spatial perspective taking and empathy, another form of perspective taking allowing to understand emotional states of others (Berthoz, 2004; Mohr et al., 2010).

There is to date only few studies on the sensorimotor foundations of third-person perspective taking. As mentioned earlier, perspective taking necessitates the translocation of one's own egocentric viewpoint into a third-person, allocentric, reference. This operation requires geometrical transformations such as translations and rotations of the viewpoint. We propose that vestibular signals play an important role in these mental transformations of the viewpoint as they have been involved in several aspects of egocentric and allocentric mental imagery (Mast et al., 2006; Dilda et al., 2012). Indeed, stimulation of the semicircular canals during whole-body rotations on a chair modified performance in a whole-body mental transformation task (van Elk and Blanke, 2013). Similar disturbing effects of vestibular stimulation on whole-body mental imagery have been reported during galvanic (Lenggenhager et al., 2008) and caloric (Falconer and Mast, 2012) vestibular stimulation. In conclusion, we propose that vestibular signals are not only involved in self-motion perception, but also in mental simulation of self-motion, which seems necessary to adopt the (visual or affective) perspective of another individual.

SELF-OTHER MIRRORING AND THE VESTIBULAR SYSTEM

Social interactions involve the observation of other bodies in motion. There is now a large body of data showing that observing someone else's body can influence sensorimotor processing at the level of one's own body. Typical examples of mirroring between the self and others are contagious yawning and itching. Electrophysiological studies have revealed that self-other mirroring influences action execution: movement execution is facilitated by the observation of a body executing the same movement (Rizzolatti and Craighero, 2004). Similarly, the observation of someone else's face being touched facilitates the detection of tactile stimuli applied to one's own face (Serino et al., 2008). These effects have been related to a mirror neuron system, a group of neurons in the parieto-frontal cortex found crucial for social cognition (Rizzolatti and Craighero, 2004; Singer and Lamm, 2009). The mirror neuron system was also activated when observing another body performing complex actions (Calvo-Merino et al., 2005), being touched (Cardini et al., 2011) or experiencing pain (Singer et al., 2004).

Recently, Lopez et al. (2013) have speculated on the existence of a *vestibular mirror neuron system*. These authors showed that vestibular self-motion perception (measured on a whole-body motion platform imposing passive motions to the body) was influenced by the observation of videos showing passive whole-body motion of a body. In addition, this effect was correlated with scores of empathy: subjects that were the most empathic were more influenced by the observation of another body being moved passively. This study revealed a social influence on self-motion perception via vestibular processing. Accordingly, we suggest that how we experience our own body motion is constantly constrained by the motion of others around us. Further behavioral and neuroimaging studies should now be conducted to reveal the underlying neural mechanisms of these effects.

BRAIN NETWORKS FOR VESTIBULAR PROCESSING AND SOCIAL COGNITION

We propose that vestibular contributions to the sensorimotor mechanisms of social cognition are mediated by vestibular projections to multisensory regions found to be crucial for self and social processing. The vestibular cortex is composed of at least ten multisensory areas (review in Lopez and Blanke, 2011). This vestibular network is centered on the Sylvian fissure and covered the temporo-parietal junction (TPJ), superior temporal gyrus, inferior parietal lobule, parietal operculum, and insula (**Figure 1A**). Other important vestibular regions have been found in the primary and secondary somatosensory cortex, intraparietal sulcus, precuneus and cingulate cortex (Bottini et al., 1994; Dieterich et al., 2003; Kahane et al., 2003; Lopez et al., 2012).

Importantly, several vestibular areas overlap those classically found involved in social cognition. We propose that the TPJ, insula and cingulate cortex are the best candidates for vestibular–social interactions. Indeed, the right TPJ and posterior insula have been involved in the sense of owning a body: damage to the posterior insula distorts ownership for the left hand and may evoke the sensation that this hand belongs to someone else (i.e., somatoparaphrenia, Baier and Karnath, 2008). Self-other distinction also depends on multisensory processing in the TPJ as transcranial magnetic stimulation applied over the right TPJ modified illusory self-attribution of non-corporeal objects in the "rubber hand illusion" (Tsakiris et al., 2008) (**Figure 1B**).

Vestibular regions were also found activated in neuroimaging studies of third-person perspective taking (**Figure 1C**). These regions included the TPJ, intraparietal sulcus and precuneus (Vogeley et al., 2004; Blanke et al., 2005; David et al., 2006; Corradi-Dell'acqua et al., 2008; Kockler et al., 2010; Lambrey et al.,

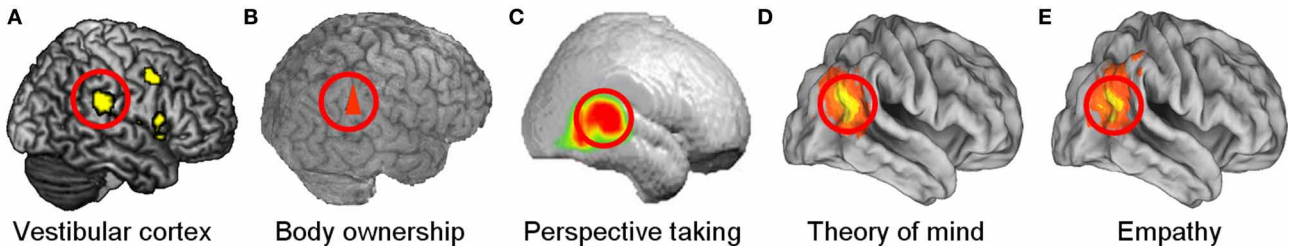


FIGURE 1 | Anatomical overlap between areas involved in vestibular processing, self-processing, and social cognition. (A) Results of a meta-analysis showing brain regions activated by various techniques of vestibular stimulation. Adapted from Lopez et al. (2012). **(B)** Temporo-parietal cortex where transcranial magnetic stimulation modified illusory self-attribution of a non-corporeal object. Adapted from Tsakiris et al. (2008). **(C)** Temporo-parietal region involved in egocentric mental rotation tasks. Reproduced from Blanke et al. (2005). **(D,E)** Brain regions involved in theory of mind and empathy. Reproduced from Decety and Lamm (2007).

2012). The same regions are more generally involved in mental imagery (Zacks, 2008), suggesting that adopting someone else's viewpoint is a mental imagery process also requiring vestibular processing. Several studies have revealed that perspective taking shares functional and anatomical bases with mentalizing or theory of mind (e.g., Vogeley et al., 2001; Frith and Frith, 2003; Aichhorn et al., 2006). We note that these important aspects of social cognition activate several vestibular areas such as the TPJ and cingulate cortex (**Figure 1D**). Finally, neuroimaging studies of empathy also revealed an implication of vestibular regions such as the anterior insula, TPJ and cingulate cortex (Decety and Lamm, 2007; Bernhardt and Singer, 2012) (**Figure 1E**). Thus, understanding mental and bodily states of others may share mechanisms with adopting someone else's visuo-spatial perspective and require vestibular processing.

CONCLUSION

We have summarized several behavioral and neuroimaging evidence from vestibular physiology and social neuroscience and have speculated on a vestibular contribution to several sensorimotor bases of social cognition. Yet, until now the vestibular cortex and neural bases of social cognition have been investigated in separate studies due to the lack of connections between the research fields of vestibular physiology and social neuroscience. We are optimistic that future research will endeavor to establish such interdisciplinary connections and propose that investigations of the multisensory foundations of social cognition should now incorporate the study of vestibular signals.

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Galvanic vestibular stimulation increases novelty in free selection of manual actions

Elisa R. Ferrè*, Kobbina Arthur and Patrick Haggard

Institute of Cognitive Neuroscience, University College London, London, UK

Edited by:
Christophe Lopez, Centre National de La Recherche Scientifique, France

Reviewed by:
Antonio Pereira, Federal University of Rio Grande do Norte, Brazil
Laurence Mouchnino, Aix Marseille Universtité – Centre National de la Recherche Scientifique, France

****Correspondence:***
Elisa R. Ferrè, Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK
e-mail: e.ferre@ucl.ac.uk

Making optimal choices in changing environments implies the ability to balance routine, exploitative patterns of behavior with novel, exploratory ones. We investigated whether galvanic vestibular stimulation (GVS) interferes with the balance between exploratory and exploitative behaviors in a free action selection task. Brief right-anodal and left-cathodal GVS or left-anodal and right-cathodal GVS were delivered at random to activate sensorimotor circuits in the left and right hemisphere, respectively. A sham stimulation condition was included. Participants endogenously generated sequences of possible actions, by freely choosing successive movements of the index or middle finger of the left or right hand. Left-anodal and right-cathodal GVS, which preferentially activates the vestibular projections in the right cerebral hemisphere, increased the novelty in action sequences, as measured by the number of runs in the sequences. In contrast, right-anodal and left-cathodal GVS decreased the number of runs. There was no evidence of GVS-induced spatial bias in action choices. Our results confirm previous reports showing a polarity-dependent effect of GVS on the balance between novel and routine responses, and thus between exploratory and exploitative behaviors.

Keywords: galvanic vestibular stimulation, exploration, exploitation, novelty, hemispheric specialization, action selection

INTRODUCTION

The exploration and exploitation trade-off is a control dilemma that involves most adaptive behaviors, and is fundamental to the relation between organism and environment (Cohen et al., 2007). This dilemma is between choosing well-known options close to the expectations (*exploitation*) and choosing new options and possibly learning more (*exploration*) (Goschke, 2000). For example, in a restaurant you can *exploit* – choose your usual meal – or you can *explore* – try whatever dish you have not had before. Thus, exploitation involves perseveration and stereotyped behavior, while exploration involves discovering new possibilities and varying choices, and potentially larger rewards (Cohen et al., 2007).

Making optimal choices in an ever-changing world includes the ability to orient in the surrounding environment (Peacocke, 1983). Therefore, we suspected that vestibular inputs could contribute to the balance between exploration and exploitation. Vestibular information is crucial to determine the relation between the body and surrounding space, and therefore forms the starting point of almost all orienting behaviors. The semicircular canals detect rotational movements of the head, while the otolith organs detect gravitational and translational acceleration. These signals contribute to orienting by modulate somatosensory inputs (Vallar et al., 1990; Ferrè et al., 2011), controlling postural and balance stability (Day and Fitzpatrick, 2005), defining spatial parameters of movement (Karnath and Dieterich, 2006) and planning motor actions (Rode et al., 1998). Primate studies revealed that vestibular input does not project to a primary vestibular cortex, but to a network of multimodal areas, notably the parieto-insular vestibular cortex (PIVC; Guldin and Grüsser, 1998). The PIVC consists of the posterior insula/retroinsular cortex in the upper or lower banks of the lateral sulcus (Guldin and Grüsser, 1998). Recent functional neuroimaging studies in humans have shown that artificial vestibular stimulation, whether galvanic, caloric, or sound-induced, activates a wide range of multimodal areas, involving the parietal and insular cortices and also the temporal cortex, putamen, and thalamus (Lopez et al., 2012). This conjunction of anatomical projections and physiological activations are broadly consistent with the view that the vestibular system acts as a basic reference system for other sensorimotor representations.

We recently found that vestibular inputs contribute to the balance between exploration and exploitation in a random number generation task (Ferrè et al., 2013). This effect was hemisphere-specific. Left-anodal and right-cathodal galvanic vestibular stimulation (GVS), which primarily activates the right hemisphere, increased randomness of sequences compared to right-anodal and left-cathodal GVS. However, vestibular stimulation also produces spatial, attentional, and arousing effects. Therefore, to investigate whether vestibular stimulation truly involves modulation of behavior selection, rather than these other independent but frequently-associated functions, we have investigated whether GVS interferes with the generation of novel vs. routinized behaviors in an endogenous action selection task. In this task, participants endogenously generated a sequence of movements, by freely

Abbreviations: GVS, galvanic vestibular stimulation; PIVC, parieto insular vestibular cortex

choosing between four possible actions, involving the index or middle finger of the left or right hand.

In discussing endogenous action selection, it is important to distinguish between "*free selection*" of single action, and generation of "*action patterns*" which exist only in the context of a sequence of actions. The trade-off between exploration and exploitation refers to sequences, or *runs,* of behavior in which the endogenous choice of any individual action is determined partly by what the participant has done before. Extreme exploitation might involve constantly repeating one action or action sequence, while extreme exploration might involve complete randomness. A pattern of action selection can therefore be analyzed quantitatively, and placed on a continuum between stereotypy and novelty. Based on our previous findings with random number generation (Ferrè et al., 2013), we hypothesized that GVS might have a polarity-dependent effect on action selection, with left-anodal and right-cathodal GVS promoting randomness/exploration rather than stereotypy/exploitation (Ferrè et al., 2013). However, it was unclear whether similar organization of vestibular influences on behavior would occur for bimanual movements as for generation of symbolic items such as numbers.

We delivered binaural GVS between the mastoids, to activate peripheral vestibular organs, i.e., both otoliths and semicircular canal afferents (Stephan et al., 2005). This induces a polarity-dependent "*virtual rotation vector*" (Day and Fitzpatrick, 2005) which can influence orientation perception and posture. More surprisingly, GVS also influences sensory and cognitive functions (Utz et al., 2010). The effects are polarity dependent. Left-anodal and right-cathodal GVS mimics an inhibition of the left and an activation of the right ear vestibular peripheral organs, decreasing the firing rate of the vestibular nerve on the left side and increasing it on the right side (Goldberg et al., 1984; Fitzpatrick and Day, 2004). In contrast, right-anodal and left-cathodal GVS induces the opposite effect. Neuroimaging studies have revealed asymmetrical cortical vestibular projections, suggesting that the core region of the vestibular network is primarily located in the non-dominant hemisphere in right-handed subjects (Dieterich et al., 2003).

Clinical observations have reported strong effects induced by vestibular stimulation on spatial attention in brain-damaged patients (Rubens, 1985; Utz et al., 2011). Recently, a contribution of vestibular information to the allocation of attention has also been suggested in healthy volunteers (Figliozzi et al., 2005). We therefore hypothesized that GVS could have spatial effects on the generation of free actions. In particular, given the specialization of the right hemisphere for spatial responding, GVS-induced activation of vestibular projections in the right hemisphere might cause an attentional shift toward the left side of the space or body (Rubens, 1985), and thus a preference for the left hand, or the leftmost digit, in action selection.

MATERIALS AND METHODS

PARTICIPANTS

Sixteen naïve right-handed paid participants volunteered (10 male, mean age 24.7 years ± 5.08 SD). Subjects with a history of visual, vestibular, or auditory disorders were excluded. Informed consent was obtained prior to participation in the experiment. The experimental protocol was approved by University College London research ethics committee. The study was designed according to ethical standards of the Declaration of Helsinki.

GALVANIC VESTIBULAR STIMULATION

Bipolar GVS was used to deliver a boxcar pulse of 1 mA via a commercial stimulator (Good Vibrations Engineering Ltd., Nobleton, ON, Canada). Carbon rubber electrodes (area 10 cm^2) were placed binaurally over the mastoid processes and fixed in place with adhesive tape. The areas of application were first cleaned with cotton wool soaked in surgical spirit, and electrode gel was applied to reduce the impedance. Left-anodal and right-cathodal ("L-GVS") was used to predominantly stimulates the right hemisphere, while the inverse polarity, left-cathodal and right-anodal configuration, "R-GVS," was used to predominantly stimulate the left hemisphere (**Figure 1B**). A "PSEUDO-GVS" sham stimulation, based on that used by Lopez et al. (2010), was applied using left-anodal and right-cathodal stimulation of the neck, 5 cm below the mastoids (**Figure 1B**). This causes a similar tingling skin sensation to real GVS, and therefore functions as a control for non-specific alerting effects.

STIMULI AND PROCEDURE

Data from each participant was gathered in a single session. Verbal and written instructions about the task were given to participants at the beginning of the session. Participants sat 50 cm from a screen and made sequences of fingers movements initiated by auditory and visual cues during GVS or PSEUDO-GVS stimulation. Electrodes for GVS and PSEUDO-GVS were placed at the beginning of the session and remained in place for the entire duration of the experiment. The electrodes and the polarity of stimulation were selected under randomized, double-blind, computer control at the start of each block.

A total of 15 blocks were administered, five for each type of stimulation (L-GVS, R-GVS, and PSEUDO-GVS). The order was randomized across participants. Before the beginning of the task, participants received a number of short training blocks. These blocks introduced and familiarized participants with the visual and auditory cues. No vestibular or sham stimulation was delivered during the training.

Each block comprised 21 trials in random order. Each trial began with a symbol "L," "R," or "=," on the center of the screen. The symbol instructed participants which hand to respond with ("=" meaning that the participant could press a button with a hand of her choice). The auditory signals referred to the *finger* for responding. A high frequency beep instructed participants to use the index finger, a low frequency beep signaled the middle finger, and a mid frequency beep signaled a free choice. The visual stimulus appeared before the auditory cue (**Table 1** and **Figure 1A**). The participant was asked to monitor the visual and auditory cues and make an appropriate keypress. For example, if the auditory tone for the index finger was heard and the "=" stimulus displayed, the participant should press a button with the index finger of whichever hand she chose. If the "free" tone was heard and a "L" was displayed on the screen, she should move either the middle or index finger of her left hand. If the "free" tone was heard and the "=" was displayed, the choice of both finger and hand was entirely free. Thus each trial was composed of a visual cue and

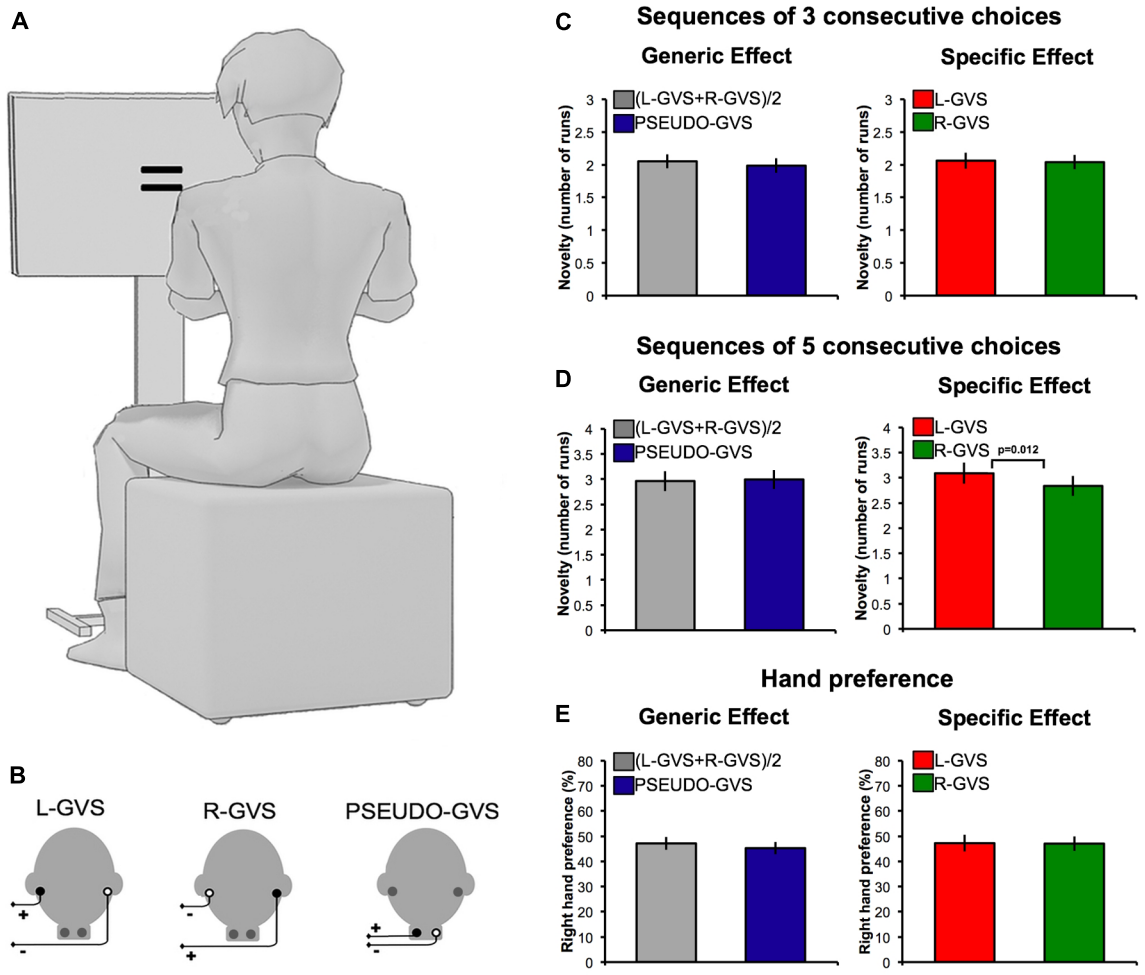


FIGURE 1 | Effects of GVS on spatial bias and novelty. (A) Experimental set-up. **(B)** GVS polarities and electrodes configurations. **(C)** Number of runs in sequences of three successive free-choices in each experimental condition. **(D)** Number of runs in sequences of five successive free-choices in each experimental condition. **(E)** Preference for right hand as a function of GVS condition.

the corresponding sequence of auditory cues. Three different trial lengths were presented, at random: single choice trial, sequences of three consecutive choices and sequences of five consecutive choices (**Table 1**).

Galvanic vestibular stimulation or PESUDO-GVS began 2,000 ms before each sequence, and ended 200 ms after the last beep. The inter-tone interval ranged between 1,000 and 1,400 ms randomly and uniformly. This cadence was adopted to discourage purely rhythmic responses and to maintain response times. The average inter-tone interval was decided after a pilot study, suggesting that 1,200 ms was sufficiently long to allow quick decisions after each imperative stimulus, whilst preventing pre-decision of which response to make.

Responses were collected via a custom keypad. The keypad was held vertically facing away from the participant (**Figure 1A**) to exclude the possibility that the lateral spatial position of the response key could influence finger choice. The index and middle fingers of left and right hands remained on the keypad throughout. Participants were instructed to maintain contact, and depress an appropriate key, within 800 ms of the visual and auditory stimuli. Ill-timed or multiple responses were also recorded. Participants were instructed to respond as quickly and accurately as possible.

Table 1 | Experimental conditions in the free action generation task.

	Visual cue = hand	Auditory cue = finger		
Single choice	Left	Index	Middle	Free
	Right	Index	Middle	Free
	Free	Index	Middle	**Free**
Sequences of 3 consecutive choices	Left	Index	Middle	Free
	Right	Index	Middle	Free
	Free	Index	Middle	**Free**
Sequences of 5 consecutive choices	Left	Index	Middle	Free
	Right	Index	Middle	Free
	Free	Index	Middle	**Free**

Possible combinations of movements during the free action generation task.

Participants were also encouraged to respond spontaneously and without pre-decision when a free choice of finger and/or hand was indicated.

DATA ANALYSIS

Because our interest focussed on vestibular modulation of action selection, we analyzed only responses obtained in the free choice conditions. Based on the distinction made above, we had different hypotheses about selection of a single action, versus sequential patterns of several actions. In particular, the trade-off between exploration and exploitation reflects the relation between each action in a sequence and the previous actions. This determines whether the sequence reflects a routinized or innovative action patterns. This relation is absent in a single instance of free action selection, and becomes progressively more important as the run of successive free actions lengthens. Therefore, we analyzed the sequences of three and five "free" consecutive choices, and we predicted that any effects of vestibular input on novelty of action choices would be stronger for longer sequences. Novelty was defined by the number of adjacent identical elements. For example, the sequence "AAAAA" comprises one run, while the "AAAAB" comprises two runs. Thus, the maximum and minimum number of runs, given five successive choices between four possible actions, are five and one, respectively.

Trials involving just one "free" choice were analyzed separately, to identify whether vestibular input generated a preference for one particular response. The percentage of right hand choices in response to free stimuli ("=" visual cues and the "free" tone) was calculated. We hypothesized that right-anodal and left-cathodal stimulation (R-GVS) would induce a right hand preference compared to left-anodal and right-cathodal stimulation (L-GVS). That is, this analysis focussed on spatial biases in individual action selection, rather than on sequential action patterns.

The number of runs in three and five-choices trials and percentage of right hand preferences were estimated for each sequence, and averaged for the three experimental conditions: L-GVS, R-GVS, and PSEUDO-GVS. We hypothesized that vestibular stimulation might influence our variables in two distinct ways (Ferrè et al., 2013), and we tested these hypotheses as planned contrasts. First, *any* activation of the vestibular system might influence free action selection independent of polarity and hemispheric effects. To test this *generic hypothesis*, we compared the average of the L-GVS and R-GVS conditions to the PSEUDO-GVS condition, for each dependent variable. Second, we hypothesized that the effects of vestibular stimulation could be *specific* to the hemisphere activated, and would therefore differ between L-GVS and R-GVS conditions.

RESULTS

The mean data in each condition are shown in **Table 2**.

GENERIC VESTIBULAR EFFECTS ON NOVEL ACTION SELECTION

The generic vestibular effect, defined as (L-GVS + R-GVS)/2, was compared to the PSEUDO-GVS condition. A 2 × 2 ANOVA with stimulation ((L-GVS + R-GVS)/2 vs. PSEUDO-GVS) and sequence length (sequences of three consecutive choices vs. sequences of five consecutive choices) was performed. This analysis revealed a predictable main effect of sequence length ($F_{(1,15)} = 92.171$, $p < 0.001$), indicating more runs of a single action choice in sequences of five consecutive choices compared to sequences of three consecutive choices, as one might expect (**Figures 1C,D**). No significant main effect of stimulation ($F_{(1,15)} = 0.086$, $p = 0.773$) or interactions between the factors ($F_{(1,15)} = 1.337$, $p = 0.266$) was found (**Figures 1C,D**).

HEMISPHERE-SPECIFIC VESTIBULAR EFFECTS ON NOVELTY GENERATION

We next compared L-GVS and R-GVS conditions. A 2 × 2 ANOVA with stimulation (L-GVS vs. R-GVS) and sequence length (sequences of three consecutive choices vs. sequences of five consecutive choices) was performed. This analysis revealed a main effect of sequence length ($F_{(1,15)} = 62.672$, $p < 0.001$). The effect of stimulation showed a trend toward conventional statistical significance ($F_{(1,15)} = 3.142$, $p = 0.097$). A significant interaction between stimulation and sequence length has been found ($F_{(1,15)} = 9.800$, $p = 0.007$). To further investigate this interaction, we directly compared L-GVS and R-GVS sequences of three and five consecutive choices. No significant difference was found in sequences of three consecutive choices ($t_{(15)} = 0.251$, $p = 0.806$; **Figure 1C**), but a significant effect emerged for sequences of five choices ($t_{(15)} = 2.86$,

Table 2 | Mean scores in each stimulation condition.

		Stimulation condition		
		L-GVS	**R-GVS**	**PSEUDO-GVS**
Measures of spatial bias	Right hand preference (%)	47.25	47.06	45.28
		(13.38)	(11.61)	(9.80)
Measures of novelty	Number of runs:	2.06	2.04	1.99
	Sequences of 3 consecutive choices	(0.49)	(0.44)	(0.44)
	Number of runs:	3.09	2.83	2.99
	Sequences of 5 consecutive choices	(0.85)	(0.78)	(0.77)

Measures of spatial bias and novelty (mean scores, SD) in L-GVS, R-GVS, and PSEUDO-GVS.

$p = 0.012$; **Figure 1D**). To investigate whether this effect reflected a benefit of L-GVS or a cost of R-GVS, we additionally compared each individual stimulation condition to PSEUDO-GVS. Neither GVS condition was significantly different from the PSEUDO-GVS ($p > 0.05$), suggesting that the effect lay in an approximately equal balance between the two hemispheric stimulations.

GENERIC AND SPECIFIC EFFECTS ON HAND PREFERENCE

Investigation of spatial effects of GVS, measured as preference for right hand actions on free-choice trials, did not reveal generic ($t_{(15)} = 0.756$, $p = 0.461$) or specific vestibular effects ($t_{(15)} = 0.054$, $p = 0.958$; **Figure 1E**).

STIMULATION EFFECTS ON TASK ERRORS

To investigate whether GVS has a specific effect on motor responses, we analyzed errors made by participants during the endogenous actions generation task. Ill-timed and multiple responses were counted across the three experimental conditions (L-GVS, R-GVS, PSEUDO-GVS). Since this analysis aimed to investigate differences between L-GVS, R-GVS, and PSEUDO-GVS on error rate, all free choice trials (one choice, sequences of three consecutive choices and of five consecutive choices) were considered. The percentage of errors was: L-GVS 4.03%; R-GVS 4.23%, PSEUDO-GVS 6.78%).

A 3 × 3 ANOVA on error rate with stimulation (L-GVS, R-GVS, PSEUDO-GVS) and sequence length (one choice, three consecutive choices and five consecutive choices) was performed. This analysis revealed a main effect of sequence length ($F_{(2,30)} = 6.396$, $p = 0.005$). Participants showed the tendency to commit more errors during single choices trials compared to trials of three consecutive choices ($t_{(15)} = 2.374$, $p = 0.031$) and five consecutive choices ($t_{(15)} = 3.354$, $p = 0.004$). Importantly, no significant effect of stimulation ($F_{(2,30)} = 1.785$, $p = 0.185$) or interaction between stimulation and sequence length ($F_{(4,60)} = 0.743$, $p = 0.567$) was found.

DISCUSSION

Here we demonstrated that vestibular input in *general* did not influence the generation of novelty in a free selection of manual responses. In contrast, *specific* polarities of vestibular input, associated with hemisphere-specific activations, had significantly different effects on free selection. Left-anodal and right-cathodal GVS increased novelty of action selection, relative to right-anodal and left-cathodal GVS, which decreased novelty. In other words, left-anodal and right-cathodal boosted the selection of different actions, shifting more often between fingers and hands movements, while right-cathodal and left-anodal promoted the repetition of the same finger movement.

GVS polarity-dependent differences in postural, sensorimotor, and cognitive functions have been demonstrated both in healthy volunteers and in brain damaged patients (Utz et al., 2010). Fink et al. (2003) used fMRI to study the effects of bipolar GVS. They found that left-anodal and right-cathodal GVS produced unilateral activation of the right hemisphere vestibular projections, while the opposite polarity, i.e., left-cathodal and right-anodal GVS, activated both left and right hemispheres (Fink et al., 2003). These results are coherent with the asymmetrical cortical vestibular representation in the right hemisphere in right-handed subjects (Bense et al., 2001; Suzuki et al., 2001; Dieterich et al., 2003; Janzen et al., 2008). Importantly, the observed hemispheric-specific effects might arise because of this cortical asymmetry, or because one polarity of GVS has stronger effects in the brain.

We suggest that the difference between L-GVS and R-GVS in action selection reflects the activation by vestibular input of a large-scale hemispheric network for behavioral control. Left and right cerebral hemispheres play different roles in novelty and cognitive routine. Goldberg and Costa (1981) formulated a *novelty-routinization* model, suggesting a strong hemispheric specialization in behavioral control. The right cerebral hemisphere is responsible for exploratory processing of new cognitive situations, particularly in the absence of any pre-existing cognitive strategy (Goldberg and Costa, 1981; Goldberg et al., 1994; Goldberg and Podell, 1995). In contrast, the left hemisphere is specialized for processing of pre-existing representation and routine cognitive strategies. Thus, right brain-damaged patients showed more repetitive behavior than patients with comparable lesions in the left hemisphere (Sandson and Albert, 1987; Goldberg et al., 1994). We suggest that the hemispheric-specific activations induced by GVS similarly influence the balance between generative and repetitive behaviors. Left-anodal and right-cathodal (L-GVS) would boost the selection of movements based on exploration, by activating the right hemisphere, while R-GVS would reduce novelty by promoting stereotyped behaviors controlled by the left hemisphere. Given the multimodal nature of vestibular cortical projections, we cannot exclude the possibility that vestibular signals reach specific frontal or parietal areas involved in the generation of motor planning. Thus, it remains unclear if our results reflect activations which produce a diffuse imbalance *between* hemispheres, or whether specific activations *within* each hemisphere are responsible.

Our results confirmed recent findings of GVS effects on random number generation (Ferrè et al., 2013). To that extent, they suggest a general, task-independent vestibular contribution to novel behavior. Left-anodal and right-cathodal GVS increased randomness compared to right-anodal and left-cathodal GVS, which decreased it (Ferrè et al., 2013). The polarity-specific effects of GVS were therefore consistent for the random number generation studied previously, and the free selection of manual responses studied here. This is particularly significant, given that the cortical areas involved in number generation and action selection are at least partly different. The generation of random numbers activated the dorsolateral prefrontal cortex, the lateral premotor cortex, the anterior cingulated, and the inferior and superior parietal cortex (Jahanshahi et al., 1998, 2000; Daniels et al., 2003). In contrast, endogenous action selection involves more medial areas, as the premotor cortex, the supplementary motor area, the intraparietal sulcus, the cingulated gyrus (Grezes and Decety, 2001). Given this similarity of GVS effects across output modalities, we suggest that vestibular stimulation may influence high-level features of action control, that go beyond a specific output system or a single cortical programming center. The balance between innovation/exploration

and perseveration/exploitation might be one such high-level parameter.

Fink et al. (2009a,b) studied changes in brain activity during novel, or creative, processing such as the generation of alternative behaviors. Individuals who scored higher on indices of originality had a stronger EEG alpha rhythm in the right than in the left hemisphere, while less original individuals showed no hemispheric asymmetry (Fink et al., 2009a). These results have been replicated using a range of different testing paradigms (Fink et al., 2009a,b) suggesting a modality independent effect of novelty on neural processing. Thus, the content of representations and behavior generated may not be crucial: almost any behavior or choice can be performed in a novel way, or repeated in a routine, preservative or stereotyped way. Our data also support this hypothesis and provide additional evidence that left and right cerebral hemispheres are differentially involved in novelty and cognitive routine generation.

Further, effects of GVS interacted with sequence length. This is also consistent with an account based on generation of novel behavior. Sequence length influences randomness for simple reasons of sampling, since the probability of generating novel choices inevitably increases with the length of the sequence (Schulz et al., 2012). Nevertheless, sequence length also affects randomness judgements, but in the opposite direction. Participants judge short sequences as more random than long sequences. Tversky and Kahneman (1971, 1974) suggested that participants try to produce a sequence of choices that is representative of a random process over a short section of behaviors. Thus, the desire to produce this representative sequence influences short sequences rather than long sequences. In line with this notion, short sequences are barely influenced by other factors. This would account for the interaction with sequence length in our data.

Although several clinical observations reported strong effects induced by vestibular stimulation in visuo-spatial attention (Utz et al., 2011), our data did not show any evidence of spatial bias. Galvanic vestibular stimulation was previously shown to interfere with spatial processing in healthy participants during spatial tasks (Dilda et al., 2012). Similarly, Figliozzi et al. (2005) demonstrated that vestibular inputs could produce spatiotopic shifts of attention. We thus hypothesized that vestibular input might shift spatial attention toward one side of the body, as a result of activating the contralateral hemisphere. In particular, attentional accounts would predict that left-anodal and right-cathodal should cause a preference for selecting the left hand. However, our data did not support this prediction. Further studies are needed to clarify the role of vestibular inputs in higher order spatial and attentional processing, in particular related to body representation. In the meantime, two possibilities exist. First, GVS may be too weak to cause spatial effects in healthy participants. Second, previous effects of vestibular stimulation in patients (Rubens, 1985) may have overestimated the vestibular role in spatial attention.

In conclusion, our results confirm previous reports showing polarity-dependent effects of GVS on the balance between novel and routine responses, and thus between exploratory and exploitative behaviors. We suggest that the vestibular-mediated balancing between exploitation and exploration may be a crucial, but neglected, element of the brain's capacity to interact with the environment.

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Epilepsy and the cortical vestibular system: tales of dizziness and recent concepts

***Russell Hewett*[1] *and Fabrice Bartolomei*[2] ***

[1] *Department of Neurology and Neurophysiology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK*
[2] *Clinical Neurophysiology and Epileptology Department, Hôpital de la Timone, Marseille, France*

Edited by:
Christophe Lopez, Centre National de La Recherche Scientifique, France

Reviewed by:
Antonio Pereira, Federal University of Rio Grande do Norte, Brazil
Marianne Dieterich, Ludwig-Maximilians-University, Germany

***Correspondence:**
Fabrice Bartolomei, Department de Médecine, Faculté de Médecine, Service de Neurophysiologie Clinique, Aix Marseille Université, CHU Timone-264 Rue Saint Pierre, 13005 Marseille, France
e-mail: fabrice.bartolomei@ap-hm.fr

Cortical representations of the vestibular system are now well recognized. In contrast, the fact that epilepsy can affect these systems, provoking transient vestibular symptoms, is less known. Focal seizures may nonetheless manifest by prominent vestibular changes ranging from mild unsteadiness to true rotational vertigo. Most often these symptoms are associated with other subjective manifestations. In pure vestibular forms, the diagnosis may be more difficult and is often delayed. The cortical origin of these symptoms will be discussed and compared with the known "vestibular" cortical representations. In addition, the existence of a specific "vestibular epilepsy" has been suggested in some publications. This condition affects young subjects with a frequent family history and most often a benign evolution, raising the possibility of a form of idiopathic epilepsy (Hewett et al., 2011).

Keywords: epilepsy, vertigo, vestibular system, EEG, cerebral cortex

INTRODUCTION

The vestibular symptoms of vertigo and disequilibrium are frequent subjective symptoms with a wide spectrum of peripheral and central causes (Neuhauser et al., 2005, 2008). Although epilepsy has been historically linked with vertigo (Gowers, 1907; Alpers, 1960; Smith, 1960; Gordon, 1999), albeit for misunderstood reasons, it has more recently been considered an extremely rare cause and often ignored by clinicians and neurologists (Brandt, 2003; Dieterich, 2007; Dieterich and Brandt, 2008).

However, as the evidence for the cortical representation of the vestibular system grows (Penfield, 1957; Guldin and Grusser, 1998; Brandt and Dieterich, 1999; Blanke et al., 2000; Duque-Parra, 2004; Best et al., 2010; Lopez and Blanke, 2011; Lopez et al., 2012), so does the evidence for vestibular symptoms occurring as a manifestation of associated focal epileptic activity (Penfield and Kristiansen, 1951; Penfield and Jasper, 1954; Kogeorgos et al., 1981; Kahane et al., 2003; Hewett et al., 2011).

Here we discuss the changing perception of the role of seizure activity in producing vestibular symptoms, and review the recent evidence that describe a pure vestibular epilepsy and raise the possibility of a idiopathic vestibular epileptic syndrome (Hewett et al., 2011).

HISTORICAL REVIEW

VERTIGO AND EPILEPSY

From ancient times the term vertigo and epilepsy have been linked conceptually and diagnostically. Bladin's excellent historical review of "epileptic vertigo" documents that in second century A.D. Arataeus stated that if vertigo proved incurable, it might be the beginning of chronic epilepsy (Bladin, 1998) whilst vertigo was also reported to be considered "a little epilepsy" (Temkin, 1994).

However, the term vertigo had a much looser definition than the illusion of surrounding or self-motion understood in present times and was considered more a manifestation of a non-specific paroxysmal cerebral disturbance (Gizzy and Diamond, 2005). It was only when analysis of the sense of motion began in the late 19th century (Baloh, 2001) did the modern understanding of vertigo as a predominantly otogenic symptom arising from the vestibular system take hold.

Vertigo and epilepsy was first formally linked and consolidated into the term "epileptic vertigo" during the pioneering years of the scientific study of epilepsy in 18th and 19th century by French clinicians. Esquirol in 1838 first introduced the concept as a grade of epileptic severity that included "vertige epileptique," "petit mal" and "grand mal" (cited in Temkin, 1994) and even with the introduction of absences to describe minor epileptic episodes, the term persisted.

Generalized seizures were considered to originate from the upper brainstem, but the condition of epileptic vertigo was thought to be localized to the hemispheres and to play a role in the mental symptoms of epilepsy. This poorly defined clinical entity developed negative connotations after research from the asylums of Paris associated aberrant behavioral episodes of the patients with brief incomplete epileptic attacks. Epileptic vertigo and thus epilepsy soon became popularly linked with the potential to suffer acute attacks of wayward potentially violent behavior (review in Bladin, 1998). The term remained in general use until the early 20th century and was accepted by many of the prolific authors of the time (Gizzy and Diamond, 2005), including Hughling Jackson:

"I believe that epileptic vertigo, epileptic petit-mal, and epileptic grand-mal are when regarded from an anatomical and physiological point of view simply differing degrees, that is to say they

depend on different strengths of discharge..." (Hughlings Jackson, 1931).

However, the definition of the condition continued to lack of clarity leading to considerable disagreement (Bladin, 1998).

VERTIGO: EPILEPSY VERSUS THE VESTIBULAR SYSTEM

In 1861 Meniere's localisation of vertigo to the inner ear drove the conceptual separation of vertigo from epilepsy (Baloh, 2001), though the shift did not occur immediately.

By the 1870's Charcot, Jackson and Gowers had recanted their early concepts and strongly accepted that most vertigo emanated from the inner ear (Gordon, 1999).

In the Borderlands of Epilepsy 1907 (Gowers, 1907), Gowers remarks on the former imprecise descriptions of vertigo: "The sense in which it is popularly used is very wide and includes every peculiar vague brain sensation, especially brief obscuration of consciousness, imperfect perception of surroundings and the like."

By the end of the 19th century, most authors had assigned vertigo to conditions other than epilepsy. If associated with epilepsy, vertigo was considered a symptom that may be felt at the onset of a seizure and even if it accompanied epilepsy, it conferred nothing of significance regarding classification or degree of severity (Bladin, 1998).

However, Gowers, being a master of medical observers, was probably the only great author in the late 19th century to still be able to consider it as a possible epileptic symptom and made great effort in making the distinction between the two entities.

"The attacks of minor epilepsy which are characterized by vertigo have to be distinguished from the other form of sudden giddiness" (Gowers, 1906).

20th CENTURY AND VESTIBULAR EPILEPSY

The term epileptic vertigo did not disappear from the literature. It continues along with epileptic dizziness, epileptic nystagmus and epileptic tinnitus as conditions purely describing the predominant symptom associated with a seizure or epilepsy (Esquirol cited in Temkin, 1994).

As the field of epileptology advanced with the widespread acceptance of a cortical basis to seizure genesis, the 20th century saw more directed effort to understand the cortical substrate for the production of vertigo and vestibular disturbance associated with focal epileptic activity.

The electrical stimulation studies in humans and monkeys in the early part of the century gave the first insight to anatomical basis of the vestibular cortex whereas more recently advances have been made by the combination of intracranial stimulation studies in medically intractable epilepsy patients and modern electroencephalography (EEG) techniques, structural and functional imaging (reviewed in Lopez and Blanke, 2011).

THE VESTIBULAR CORTEX IN EPILEPSY

In comparison to the wealth of data collected with regards to the visual and auditory cortices, less is known of the vestibular cortical representation and the processing of vestibular information. Data from tracer and electrophysiological studies on non-human primates have demonstrated multiple distinct vestibular cortical areas (Guldin and Grusser, 1998) with a parieto-insular vestibular cortex (PIVC) as a proposed core vestibular region. This can be directly been compared to clinical work and neuroimaging in humans (Lopez and Blanke, 2011), as well as recent meta-analyses of neuroimaging studies that more specifically propose the parietal operculum and posterior insula as candidates for the primary vestibular cortex (Lopez et al., 2012; zu Eulenburg et al., 2012).

In particular focal brain stimulations in epileptic patients have added to the mounting evidence of human vestibular cortical representation.

STIMULATION STUDIES IN EPILEPTIC PATIENTS AND VESTIBULAR SYMPTOMS

During electrical cortical stimulation in awake patients undergoing brain surgery Foerster demonstrated that stimulation of the intraparietal sulcus elicited full body rotations in space (Foerster, 1936), whereas a few years later stimulation of the superior temporal gyrus in patients operated on for focal epilepsy was associated with the sensations of "swinging, spinning," "sinking feeling" and "head jumping up and down" (Penfield and Kristiansen, 1951; Penfield and Jasper, 1954; Penfield, 1957)

More recently a new insight has been gained from a retrospective systematic study of intracranial electrical stimulation using depth electrodes in 44 refractory epilepsy patients (Kahane et al., 2003). It reported a wide distribution of anatomical sites from which vestibular sensations were electrically induced though confirmed that most sites were in the temporal and parietal areas. The authors suggested the presence of a human temporo-peri-Sylvian vestibular cortex (TPSVC), a possible equivalent to the monkey's polysensory PIVC, but involving the insula less as stimulation of the insula infrequently evoked conscious vestibular sensations (Isnard et al., 2004). Stimulation of the parietal lobe more posteriorly, in area 39 near the angular gyrus has elicited non-specific vestibular sensations (Blanke et al., 2002). The angular gyrus has been previously proposed as the "epicenter of the vestibulo-psychic area" on the basis of lesional studies in epileptic patients (Smith, 1960). The data obtained from human stimulation studies are summarized in **Figure 1**.

The authors of the large retrospective intracerebral stimulation study were able to propose anatomical correlates to certain types of vestibular sensations (Kahane et al., 2003). Pitch plane illusions were mainly elicited from the parietal operculum and yaw plane illusions from the temporal cortex. Translational linear illusions were more frequently elicited by stimulation of the mesial structures, in particular the mesial parietal cortex. In a separate case report, stimulation of the right paramedian precuneus also reproduced the epileptic linear self-motion perception (Wiest et al., 2004). Another study using subdural grids, induced rotational and swaying bidirectional vestibular sensations by stimulating two adjacent sites at the anterior part of the intraparietal sulcus (Blanke et al., 2000).

This could suggest a three-dimensional coding of spatial information according to anatomical site, and the increasing complexity of bidirectional vestibular sensations could reflect higher level processing such as shown with the progressive increase in complexity the hierarchical organization of the visual and auditory systems.

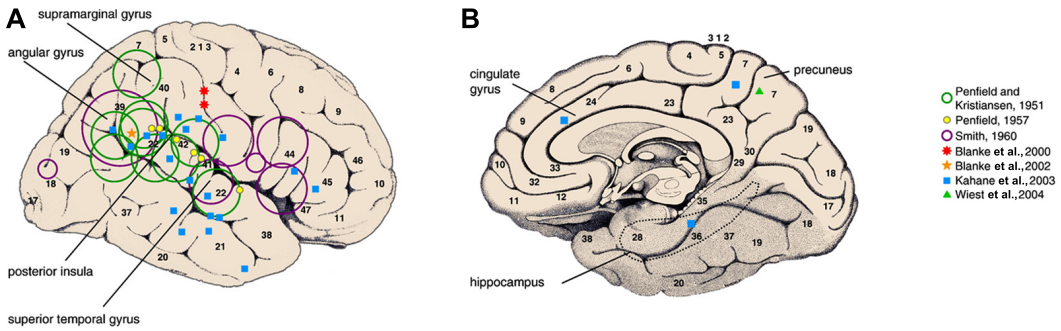


FIGURE 1 | Vestibular areas defined from direct electric cortical stimulations in epileptic patients. Green and purple open circles represent the location of epileptogenic lesions responsible for vestibular sensations. Filled symbols represent the site at which focal electrical stimulation of the cortex evoked vestibular illusions in awake epileptic patients(reproduced from Lopez and Blanke, 2011).

Although this data contributes considerably to the understanding of the vestibular system a caveat to the stimulation on epileptic cortices is the possibility of cortical plasticity associated with recurrent seizures. This could explain the inter-individual variability in the studies.

FOCAL SEIZURES AND VESTIBULAR SYMPTOMS

As well as the cortical stimulation studies, data has been gained by the close study of the electroclinical characteristics of focal seizures associated with vestibular dysfunction. Early studies in the 20th century (Penfield and Kristiansen, 1951; Smith, 1960) localized focal epileptic discharges associated with vertigo to the superior temporal gyrus and the temporo-parietal cortex.

A particularly detailed clinical study of 120 patients revealed the commonest symptoms were the sense of rotational vertigo predominantly in the yaw and roll planes, linear translational illusions or a combination (Smith, 1960). More complex vestibular dysfunctions such as the sensation of floating, the anticipation of spinning and unsteadiness were also described supporting the theory of higher levels of organization (**Figure 2**).

More recently focal seizure activity associated with vestibular illusions of rotation involving of the temporo-parieto-occipital (TPO) junction has been demonstrated by stereotactic EEG (SEEG) recordings (Barba et al., 2007) and in a case using interictal SPECT and scalp EEG (Jaffe et al., 2006). Parietal seizures have been known to be often associated with vestibular sensations (Salanova et al., 1995), but in a recent SEEG study of the epileptogenic networks underlying parietal lobe seizures, vestibular sensations were associated with seizures arising from the superior parietal region (Bartolomei et al., 2011), in keeping with stimulation studies of intraparietal sulcus eliciting vestibular responses (Blanke et al., 2000). Parietal seizures could also elicit vestibular symptoms by interfering with areas associated with representation of the body in space (Blanke et al., 2000).

Vestibular symptoms are occasionally reported in other localisations, particularly in frontal lobe seizures (Lopez et al., 2010).

Focal seizures associated with vestibular sensations arising from these multiple distinct cortical areas is in keeping with current theories of a widespread vestibular multisensory cortical network (Lopez and Blanke, 2011).

PURE "VESTIBULAR EPILEPSY": A SEPARATE EPILEPTIC SYNDROME?

It is well recognized that vestibular symptoms commonly accompany more epileptic seizures, however, it is rare to have purely vestibular symptoms (Berkovic and Crompton, 2010). Despite the current perceived rarity of its existence attempts have been made since Gower to describe "pure" vestibular seizures (Alpers, 1960). In their report about "epileptic vertigo," Jepsen and Pedersen (1956) reported two patients among 14 with pure vestibular seizures.

Two recent studies have attempted to more completely describe the diagnostic features of non-lesional epilepsies where the vestibular symptoms are the predominant features (Kogeorgos et al., 1981; Hewett et al., 2011; **Table 1**)

CLINICAL FEATURES

Vestibular epilepsy is characterized by focal seizures with vestibular symptoms as either the sole or predominant feature. The vestibular symptoms can range from mild disequilibrium to frank vertigo in any plane of action (yaw, pitch, roll, linear), however, it is rare however to have purely vestibular symptoms. The most common accompanying symptoms are nausea or vomiting and tinnitus (Brandt, 2003; Hewett et al., 2011) but other well documented symptoms including ipsilateral and contralateral parasthesias, olfactory and gustatory hallucinations, depersonalisation, epigastric discomfort, anxiety and deja-vu which almost certainly reflect local seizure propagation (Kogeorgos et al., 1981).

Body or head and eye rotation with or without nystagmus is considered to be frequent in some descriptions, however this is not noted in the two published case series (Kogeorgos et al., 1981; Hewett et al., 2011).

A short period of altered consciousness has been considered a central characteristic of the epilepsy (Alpers, 1960). 50% of patients in series described by Kogeorgos et al. (1981) had brief "absences" with 23% having generalized tonic-clonic seizures (GTCS). 65% of patients had full loss of consciousness with a fall in the recent case series, though only 21% had GTCS (Hewett et al., 2011). In this series, a cardiogenic syncope (two had paroxysmal atrial fibrillation, and one with transient asystole during a focal seizure) or a vasovagal syncope (positive tilt table test)

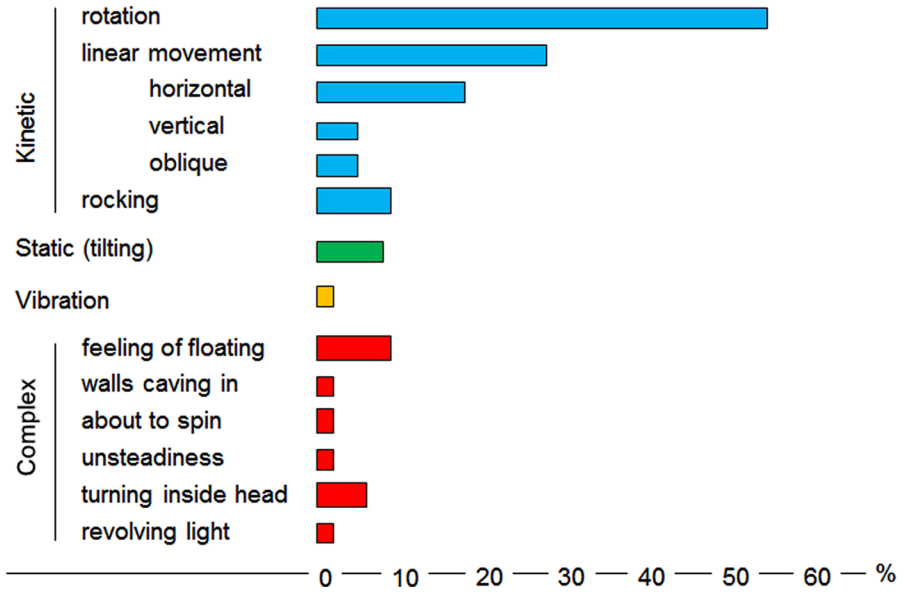


FIGURE 2 | Vestibular symptoms as reported in the Smith's (1960) study (see comments in the text).

Table 1 | Comparison between two series of patients with pure vestibular epilepsies.

	Kogeorgos et al. (1981)	Hewett et al. (2011)
Age at onset (mean, years)	25	26
Sex ratio M/F	1/1	2/1
Familial history	20%	28%
Febrile Sz	7%	-
Vestibular symptoms	100%	100%
Rotational	47%	78%
GTCS	23%	28%
Other clinical pictures	"Absences"	Neurocardiogenic syncopes, falls
Neuroimaging	N (CT-scan)	N (MRI)
EEG	Temporal posterior	TPO junction
Side predominance	Left	Right
Therapeutic response	Good	Good

Sz, seizure; GTCS, generalized tonic-clonic seizures; N, normal; TPO, temporo-occipito-parietal.

may have accounted for some of the loss of consciousness and fall. This association may just suggest epilepsy with concurrent cardiovascular disease, but in this young age group, it may suggest a link between the two conditions, particularly a predisposition for vasovagal hyperactivity.

The duration of seizures can be variable but is usually brief lasting a few seconds, though there are some patients reporting seizures lasting many minutes (Hewett et al., 2011). The symptoms are typically paroxysmal beginning suddenly and unless the seizure secondarily generalizes they usually discontinue abruptly. In cases of pure vestibular symptomatology these features can be particularly helpful in differentiating from other vertiginous diagnoses (see below; Alpers, 1960; Brandt, 2003).

ELECTROENCEPHALOGRAPHY

A diagnosis will be heavily supported by positive EEG findings and lateral temporal epileptic foci are frequent (Alpers, 1960; Brandt, 2003).

In the series described by Kogeorgos et al. (1981) an abnormal interictal EEG was a major criterion for the diagnosis. 28/30 had a temporal or bitemporal abnormalities, in some associated with generalized seizure discharges. There was a left temporal emphasis in 50%, right in 25% and bitemporal in 20%. The other two had atypical generalized patterns.

In the series described by Hewett et al. (2011), the predominant features on interictal scalp EEG were abnormalities over the parietal or TPO areas (**Figure 3**). Many of these activities are close in their morphology and topography to lambda waves and are therefore difficult to distinguish from physiological activity. A right side predominance was also found in this series.

FAMILY HISTORY

A family history of epilepsy was elicited in 20% (Kogeorgos et al., 1981) and 29% (Hewett et al., 2011) had some form of family history but none with first-degree relative. A genetic link is therefore possible in these cases and a family history of epilepsy is a helpful feature in differentiating from the other vestibular syndromes.

MANAGEMENT

Vestibular seizures are considered to respond well to anti-epileptic medication (Brandt, 2003). In the oldest series, over half of the patients had complete remission with phenytoin or carbamazepine with a considerable reduction in the frequency and severity of

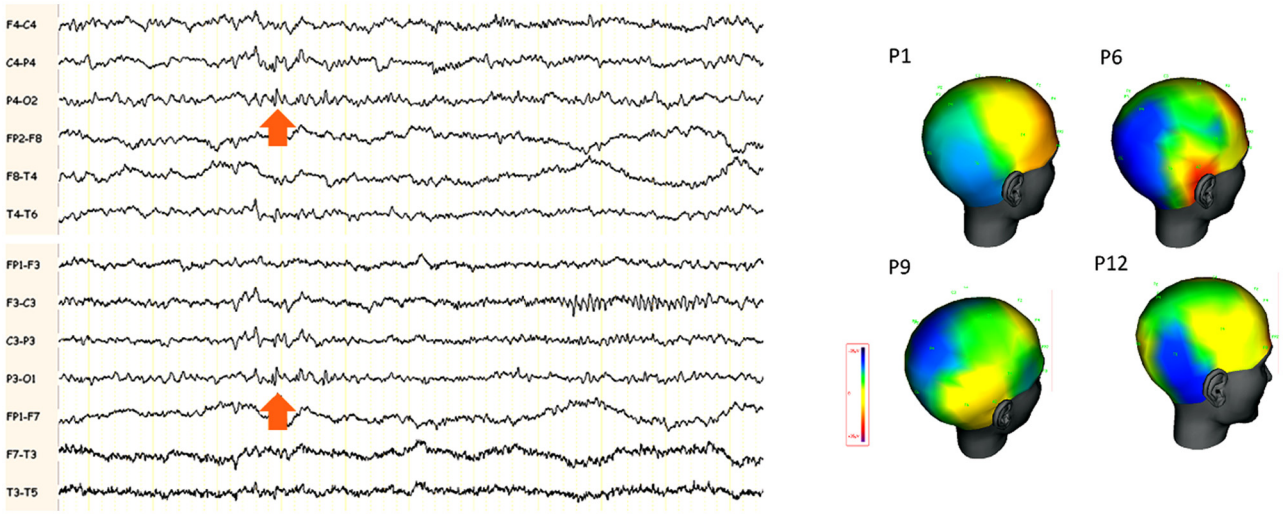


FIGURE 3 | (A) Example of scalp EEG with interictal abnormalities in the posterior electrodes in a patient with "benign TPO junction epilepsy." The arrows indicate small spikes and waves around the electrodes P3 and P4 bilaterally. **(B)** Amplitude cartography using coherence (deltamed-natus) software in four patients with benign TPO junction epilepsy (adapted from Hewett et al., 2011). One representative single interictal spike is shown. Note the negative distribution (in blue) over the TPO region, maximal in T6, P4 and O2 in the four patients.

attacks with the remainder who complied (Kogeorgos et al., 1981). All the patients that complied to treatment (12/14) in the other case series were seizure free at time of publication on either mono or dual therapy with more modern medication (Hewett et al., 2011).

DIFFERENTIAL DIAGNOSIS

Vestibular syndromes

The short duration of the symptoms and abruptness of recovery would exclude peripheral vestibular syndromes such as Meniere's disease or vestibular neuritis.

Basilar/vestibular migraine is considered to be the most common cause of spontaneous episodic vertigo. The duration varies from seconds to days, usually lasting minutes to hours, and they mostly occur independently of headaches (Bisdorff, 2011). Interestingly the anticonvulsant Lamotrigine seems to be more effective for the vertigo attacks than the headaches (Cha, 2010) raising the possibility of misdiagnosis or overlap between vestibular migraine and epilepsy.

At least six primary episodic ataxia (EA) syndromes have been described (Jen et al., 2007), of which EA1 and EA3 could mimic vestibular epilepsy most closely.

EA1 presents with brief episodes of ataxia lasting seconds to minutes and phenotypic variants combine partial epilepsy. EA3 presents with episodic vertigo, tinnitus and ataxia typically lasting minutes. Interestingly, there is clear overlap in clinical features between EA3 and migraine-associated vertigo.

Transient ischaemic event in vertebrobasilar territory, and the rare paroxysmal brainstem attacks with ataxia/dysarthria in MS can all mimic vestibular seizures due to their brief duration, but associated brainstem dysfunction aids in their differentiation (Brandt, 2003; Dieterich, 2007). Variability of the symptoms and accompanying functional symptomatology can support diagnosis of psychogenic cause (Cherchi, 2011) and phobic postural vertigo is commonly associated with an obsessive personality (Brandt, 1996).

Other seizures

A vestibular seizure is not difficult to distinguish from vertiginous syndromes if accompanied by other epileptic features, though other epileptic seizures need to be considered. Limbic seizures arising from the mesial temporal lobe present with prominent psychic (perceptual illusions, mnemonic or emotional) or autonomic features that can either be associated with vertiginous syndromes or could be mistaken by the patient to be vestibular symptoms (Maillard et al., 2004). Rotatory seizures (volvular epilepsy or circling epilepsy) are characterized by paroxysmal repetitive walking in small circles, the direction of rotation usually contraversive to the epileptic focus and preceded by versive movements of the head and body in the same direction (Brandt, 2003).

Vestibulogenic seizures

Vestibular epilepsy should not be confused with the distinct classical and historically defined condition of "vestibulogenic epilepsy." This is a variety of sensory-evoked epilepsy caused by an inner ear disorder or provoked by peripheral labyrinthine stimulation (Brandt, 2003). These are considered to be example of a reflex epilepsy. In extremely rare cases seizures with only vestibular manifestations and EEG discharges localized into the temporo-parietal region are triggered by vestibular stimuli (Gizzi and Diamond, 2005). However, this mode of provocation is probably not specific in the majority of cases (Karbowski, 1989).

Presyncopal symptoms

A major differential to consider and separate from epileptic vestibular symptoms are presyncopal symptoms.

Patients describing genuine vaso-vagal or cardiogenic pre-syncopal symptoms will commonly use the term dizziness and may confuse these with vestibular symptoms (Wieling et al., 2009). Strict clarification is necessary. This is challenging as the term dizziness has also been attributed to many different sensations that can be associated with vestibular seizures, e.g. apprehension, mental confusion, pressure in the head, tinnitus, gastrointestinal awareness, nausea, "auditory disturbance," and blindness. Furthermore some patients, as in the most recent series, do have true syncopal manifestations associated with vestibular epilepsy (Hewett et al., 2011).

CONCLUSION: AN UNDER RECOGNIZED FORM OF EPILEPSY?

Vestibular epilepsy can offer difficulty in recognition and is still perceived as extremely rare (Dieterich, 2007; Crompton and Berkovic, 2009) unless there are clear epileptic features, diagnosis is often delayed. In the most recent case series, the average delay in diagnosis following onset of symptoms was 4 years (Hewett et al., 2011) and although 11/14 patients had other features of seizure activity, a majority (Brandt, 2003) were initially seen by otorhinolaryngologist or cardiologist before review by a neurologist.

When diagnosed, the vestibular seizures have been regarded as a heterogenous group of partial seizures. However, this recent case series of patients describe a series of adolescents and adults who share defining electroclinical characteristics of a non-lesional pharmacoresponsive epilepsy manifesting as prominent vestibular disturbances. Many of these characteristics are shared by the larger case series described 30 years earlier (Kogeorgos et al., 1981).

Given the relatively young onset, the family history, and relatively "benign" nature of these epilepsies, we propose that they may represent more than just a number of heterogeneous group of cryptogenic partial epilepsies. Although further characterisation is required, this raises the possibility of a form of idiopathic epilepsy. We recently proposed the term "benign temporo-parieto-occipital junction epilepsy with vestibular disturbance" to characterize this condition (Hewett et al., 2011).

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Vestibular pathways involved in cognition

***Martin Hitier*[1,2,3,4]*, *Stephane Besnard*[1] *and Paul F. Smith*[2]**

[1] Inserm, U 1075 COMETE, Caen, France
[2] Department of Pharmacology and Toxicology, Brain Health Research Center, University of Otago, Dunedin, New Zealand
[3] Department of Anatomy, UNICAEN, Caen, France
[4] Department of Otolaryngology Head and Neck Surgery, CHU de Caen, Caen, France

Edited by:
Christophe Lopez, Centre National de La Recherche Scientifique (CNRS), France

Reviewed by:
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Vladimir Marlinski, Barrow Neurological Institute, USA

***Correspondence:**
Martin Hitier, Department of Otolaryngology Head and Neck Surgery, CHU de Caen, Av. Côte de Nâcre, Caen, Normandy 14000, France
e-mail: mart1_hit@yahoo.fr

Recent discoveries have emphasized the role of the vestibular system in cognitive processes such as memory, spatial navigation and bodily self-consciousness. A precise understanding of the vestibular pathways involved is essential to understand the consequences of vestibular diseases for cognition, as well as develop therapeutic strategies to facilitate recovery. The knowledge of the "vestibular cortical projection areas", defined as the cortical areas activated by vestibular stimulation, has dramatically increased over the last several years from both anatomical and functional points of view. Four major pathways have been hypothesized to transmit vestibular information to the vestibular cortex: (1) the vestibulo-thalamo-cortical pathway, which probably transmits spatial information about the environment via the parietal, entorhinal and perirhinal cortices to the hippocampus and is associated with spatial representation and self-versus object motion distinctions; (2) the pathway from the dorsal tegmental nucleus via the lateral mammillary nucleus, the anterodorsal nucleus of the thalamus to the entorhinal cortex, which transmits information for estimations of head direction; (3) the pathway via the nucleus reticularis pontis oralis, the supramammillary nucleus and the medial septum to the hippocampus, which transmits information supporting hippocampal theta rhythm and memory; and (4) a possible pathway via the cerebellum, and the ventral lateral nucleus of the thalamus (perhaps to the parietal cortex), which transmits information for spatial learning. Finally a new pathway is hypothesized via the basal ganglia, potentially involved in spatial learning and spatial memory. From these pathways, progressively emerges the anatomical network of vestibular cognition.

Keywords: vestibular system, neuroanatomy, cognition, hippocampus, vestibular cortex, spatial orientation, basal ganglia, theta

INTRODUCTION

The vestibular system senses angular and linear acceleration of the head in three dimensions and is responsible for generating vestibulo-ocular and vestibulo-spinal reflexes that stabilize the visual image on the retina and adjust posture (respectively), during head movement. However, this sensory system also has a role in cognition. Anyone who has experienced vestibular-induced vertigo will admit that spatial perception and cognition dramatically change when the environment seems to be spinning around.

Research in both animals and humans has revealed the role of the vestibular system in cognition (see for review Smith et al., 2010): it concerns self-motion perception, bodily self-consciousness, spatial navigation, spatial learning, spatial memory and object recognition memory (Liu et al., 2004; Zheng et al., 2004; Angelaki and Cullen, 2008; Zheng et al., 2006, 2009; Baek et al., 2010; Besnard et al., 2012; Smith, 2012).

The anatomical substrates of these cognitive functions have been studied with neuronal tracers, electrophysiology, immunohistochemistry, functional imaging and also indirectly through behavioral studies. Four different pathways have been proposed to transmit vestibular information to cortical centers involved in cognition: (1) the vestibulo-thalamo-cortical pathway; (2) a pathway from the dorsal tegmental nucleus via the lateral mammillary nucleus, the anterodorsal nucleus of the thalamus to the entorhinal cortex; (3) a pathway via the nucleus reticularis pontis oralis, the supramammillary nucleus and the medial septum to the hippocampus; and (4) a possible pathway via the cerebellum, and the ventral lateral nucleus of the thalamus (perhaps to the parietal cortex) (see Smith, 1997; Smith et al., 2005; Hüfner et al., 2007 for reviews).

Nevertheless, some segments of these pathways are only hypothesized, with no real proof of vestibular input involved, while the validity of other segments is reinforced by recent studies (e.g., Aravamuthan and Angelaki, 2012; Clark et al., 2012; Shibata and Honda, 2012; Chen et al., 2013; Yakusheva et al., 2013).

Abbreviations: ADN, Anterior Dorsal Nucleus of the thalamus; AHV, Angular Head Velocity cells; HD cell, Head Direction cell; MEC, Medial Entorhinal Cortex; PIVC, Parieto-Insular Vestibular Cortex; PoS, Postsubiculum = dorsal portion of the presubiculum; PPTg, Pedunculopontine Tegmental Nucleus; Theta, hippocampal theta rhythm; VPS, nucleus ventralis posterior superior (thalamus); VPP, nucleus ventralis posterior pars posterior (thalamus); VNC, Vestibular Nuclear Complex.

Here we will review and analyze the current knowledge relating to the vestibular pathways involved in cognition. We begin by describing the cortical areas involved in vestibular cognition (**Figure 1**), then the four probable main pathways transmitting vestibular inputs to those cortices (**Figure 2**).

COGNITIVE FUNCTIONS AND VESTIBULAR CORTICES

The vestibular cortical projection areas can be defined as the cortical areas activated during selective stimulation of the vestibular system (e.g., whole body rotation in darkness, excluding visual and proprioceptive stimulation). Studies in rodents, cats, monkeys or humans have identified nine major vestibular cortical areas, most of them playing a specific role in spatial cognition (see Shinder and Taube, 2010 for a review).

PARIETO-INSULAR VESTIBULAR CORTEX (PIVC) AND TEMPORO-PARIETAL JUNCTION

The Parieto-Insular Vestibular Cortex (PIVC) is usually described as the principal vestibular cortex because 1/3 of its neurons are sensitive to vestibular stimulation (Grüsser et al., 1982; Akbarian et al., 1988; Grüsser et al., 1990a; see Lopez and Blanke, 2011 for review). The PIVC is more precisely located in the lateral sulcus, on its temporal lip in Platyrrhini (e.g., Squirrel Monkey) but on its parietal lip in Catarrhini (e.g., Macaque). In cats the PIVC would be partially represented by the Anterior Supra-Sylvien cortex (see Lopez and Blanke, 2011 for review). In humans the exact location of the PIVC is not clear, but fMRI studies show activation of the temporo-parietal junction (i.e., the superior temporal gyrus, posterior insula, inferior parietal lobule) or more precisely the area OP2 of the parietal opercula (zu Eulenburg et al., 2011; see Lopez and Blanke, 2011 for review). PIVC neurons also receive proprioceptive input, mostly during body movement independent of head movement. This allows the PIVC to integrate body motion in reference to the vestibular inputs (Robinson and Burton, 1980; Akbarian et al., 1988; Grüsser et al., 1990b; Schneider et al., 1993; Björnsdotter et al., 2009; see Shinder and Taube, 2010 for review; **Figure 1**). This representation of body movement is called idiothetic (i.e., egocentric) because the reference (e.g., vestibular input) is in the body, contrary to allothetic (i.e., allocentric) representations, where the reference is part of the environment (e.g., visual cues). In humans, the temporo-parietal junction could also integrate vestibular input involved in mental rotation tasks in an egocentric reference frame (Falconer and Mast, 2012).

ANTERIOR PARIETAL CORTEX

As early as 1966, vestibular input was identified in the anterior parietal somatosensory cortex (Fredrickson et al., 1966). Three different areas have been identified: (1) area 2v is part of area 2, posterior to the somatosensory area of the hand and the mouth (monkey and cat) (Büttner and Buettner, 1978); (2) the area 3aHv is located within the 3a somatosensory field of the hand and arm, at the anterior bank of the central sulcus (squirrel monkey, cat) (Ödkvist et al., 1974); and (3) the area 3aNv is also a part of area 3a, but where the neck is represented and extends anteriorly into the motor cortex (area 4) (Guldin et al., 1992; see Guldin and Grüsser, 1998 for review). About 30 to 50% of the neurons in 3aNv are responsive to vestibular stimuli (see Guldin and Grüsser, 1998 for review). Functional imaging in humans shows activation of the anterior part of the intraparietal sulcus and primary somatosensory cortex, arguing for a human equivalent of area 2v, 3aHv and 3aNv. However, the anterior part of area 7 in humans (7 ant) may also be the homolog of area 2v in the monkey brain (see Brandt and Dieterich, 1999 for review). The anterior parietal vestibular cortex is thought to be a center of integration of vestibular input and somatosensory information from the head, neck and upper limbs. (Ödkvist et al., 1974; Zarzecki et al., 1983; Akbarian et al., 1993; Guldin et al., 1993; Akbarian et al., 1994) This integration possibly plays a role in differentiating self from object motion (see Shinder and Taube, 2010 for review; **Figure 1**).

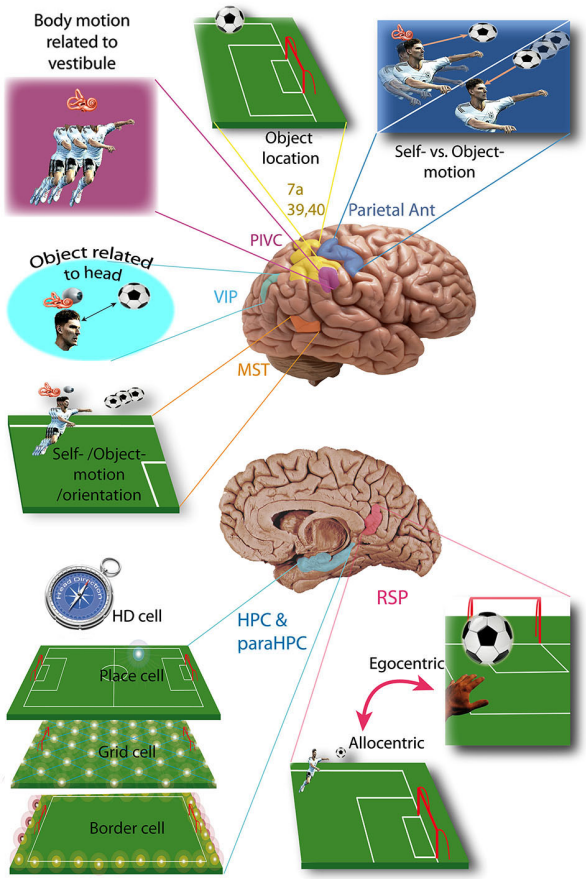


FIGURE 1 | Vestibular cortices and spatial cognition. Vestibular cortices involved in spatial cognition, illustrated in a soccer player: HD cell, head direction cell; HPC, hippocampus; MST, medial superior temporal area; ParaHPC, parahippocampal cortex; Parietal Ant, parietal anterior cortex; PIVC, parieto-insular vestibular cortex; RSP, retrosplenial cortex; VIP, ventral intraparietal area; 7a, 39, 40 Brodmann area. (References in the text).

POSTERIOR PARIETAL AND MEDIAL SUPERIOR TEMPORAL CORTICES

The posterior parietal cortex contains two major areas involved in vestibular cognition: the ventro-intraparietal cortex and area 7a. The ventro-intraparietal cortex is located in the fundus of the intra-parietal sulcus, neighboring the medial and lateral intraparietal areas (Bremmer, 2005). The area 7a (i.e., area PG)

represents the medial part of Brodmann area 7 in the inferior parietal lobule (Andersen et al., 1990). Functional imaging in humans during vestibular stimulation shows activation of the inferior parietal lobule in area 39 and 40, which could therefore correspond to area 7 in monkeys (Bottini et al., 1994; Vitte et al., 1996; Suzuki et al., 2001; see Lopez and Blanke, 2011 for review). Area 7 in monkeys must be differentiated from area 7 in humans, which is also activated by vestibular stimulation but located in the lateral superior parietal lobule (Vitte et al., 1996; Suzuki et al., 2001). The posterior parietal cortex is known as a multimodal center playing a key role in spatial representation and encodes precise self-motion and acceleration states (Andersen, 1997; Whitlock et al., 2012). In the ventro-intraparietal cortex, about half of the neurons receive vestibular input, and almost all of them receive visual input while less than half receive somatosensory input (Bremmer, 2005). From these inputs the ventro-intraparietal cortex creates a representation of space within about 1 meter of the subject and integrates visual object location information relative to the head (e.g., an approaching target to the face) (see Colby and Goldberg, 1999 and Bremmer, 2005 for review). It may also suppress reflex movement during active movement (Klam and Graf, 2006). On the other hand, area 7a in the inferior parietal lobule receives very little vestibular input and contributes to an allocentric representation of visual objects in the environment (Snyder et al., 1998; Chafee et al., 2007; Crowe et al., 2008).

Another allocentric representation of space occurs in the medial superior temporal cortex of monkeys, which detects self-motion from vestibular and visual inputs, and distinguishes them from object motion and updates spatial orientation (Geesaman and Andersen, 1996; Duffy, 1998; Gu et al., 2006; Fetsch et al., 2007; see Shinder and Taube, 2010 for review). In humans the equivalent of the medial superior temporal cortex is probably located in Brodmann area 37 of the middle temporal gyrus (Bense et al., 2001; Stephan et al., 2005; **Figure 1**).

CINGULATE GYRUS AND RETROSPLENIAL CORTEX

The "vestibular cingulate region" corresponds to the anterior part of the cingulate gyrus (area 24), showing a strong connection with the PIVC, area 3a and the visual posterior sylvian area in monkeys (Guldin et al., 1992; see Guldin and Grüsser, 1998; Lopez and Blanke, 2011 for reviews). In humans, functional imaging during caloric vestibular stimulation demonstrated activation of the anterior and posterior cingulate gyrus, which are reciprocally connected (Nieuwenhuys et al., 2008). Another study showed activation of the retrosplenial cortex (area 29 and 30) (Vitte et al., 1996), which plays a key role in navigation and path integration (Cooper and Mizumori, 2001; Cooper et al., 2001; Whishaw et al., 2001). The retrosplenial cortex could also transform a representation from allocentric to egocentric (and vice versa) (see Vann et al., 2009 for review; **Figure 1**).

HIPPOCAMPAL AND PARAHIPPOCAMPAL CORTICES

The hippocampus and parahippocampal area (i.e., entorhinal, perirhinal and postrhinal cortices) integrate cognitive maps (see McNaughton et al., 1996, 2006 for reviews). The construction of these maps is based on place cells, border cells, head direction cells (HD cells) and grid cells which are all predominant in these brain areas. These cell types have been extensively studied, with most work being performed in rodents. Place cells are defined as having an activity highly correlated with the location of the subject in a specific area of the environment (O'Keefe, 1976; **Figure 1**). They are found in CA1 (pyramidal cells), CA3 of the hippocampus (pyramidal cells), dentate gyrus (granule cells), subiculum (pyramidal cells), parasubiculum, entorhinal and postrhinal cortices (Brown and Taube, 2007). There is some evidence for place cells in the human hippocampus and they are associated with spatial view cells in the parahippocampal region (Ekstrom et al., 2003). However, some of these cells responded to place and view, which makes them substantially different from the usual definition of a place cell. Nonetheless, Ekstrom et al. (2003) estimated that approximately 11% of the recorded cells responded to place but not view and these were most common in the hippocampus. Contrary to place cells, grid cells do not fire in only one location but in multiple specific locations forming an equilateral triangle grid-like pattern (Fyhn et al., 2004; Hafting et al., 2005; **Figure 1**). Grid cells have been found so far in the lateral and medial entorhinal cortices of rodents and recently humans (Fyhn et al., 2007; Jacobs et al., 2013) and provide a two-dimensional metric for space (Hafting et al., 2005). However, the putative grid cells in humans were demonstrated to exhibit grid-like firing during a virtual navigation task, and therefore this is quite different to the grid cells recorded in rodents during actual spatial navigation (Jacobs et al., 2013). Border cells fire at the boundaries of an environment (**Figure 1**). They are found in all layers of the medial entorhinal cortex, the parasubiculum and the postsubiculum (PoS; Solstad et al., 2008; Clark and Taube, 2012). The fourth type of cell, the HD cells, are characterized by the highest rate of firing when the head is facing a narrow range of directions. They have been studied mostly in rodents, but also in monkeys and are found in numerous cortical locations including the PoS and CA1 of the hippocampus and also several subcortical nuclei (cf: the pathway from the dorsal tegmental nucleus via the lateral mammillary nucleus, the anterodorsal nucleus of the thalamus to the entorhinal cortex, below).

Vestibular input appears to be fundamentally important for place and HD cells, as inactivation of the vestibular system leads to the disruption of location-specific firing in hippocampal place cells and the direction-specific discharge of thalamic and PoS HD cells (Stackman and Taube, 1997; Stackman et al., 2002; Russell et al., 2003). Moreover, electrical stimulation of different vestibular sensors induces field potentials in the guinea-pig hippocampus (CA1, CA2) (Cuthbert et al., 2000). Also electrical stimulation of the medial vestibular nucleus increases the firing rate of CA1 complex spiking cells (putative place cells) in rats (Horii et al., 2004). In humans, functional imaging during vestibular stimulation demonstrates activation or inactivation of the hippocampal and parahippocampal areas (Bottini et al., 1994; Vitte et al., 1996; Suzuki et al., 2001; Deutschländer et al., 2002; Fasold et al., 2002; Dieterich et al., 2003). Most importantly, patients with chronic bilateral vestibular deficits demonstrate bilateral hippocampal atrophy and spatial memory impairment (Brandt et al., 2005).

All of these results emphasize the fundamental role of vestibular inputs in integrating different maps of the same environment

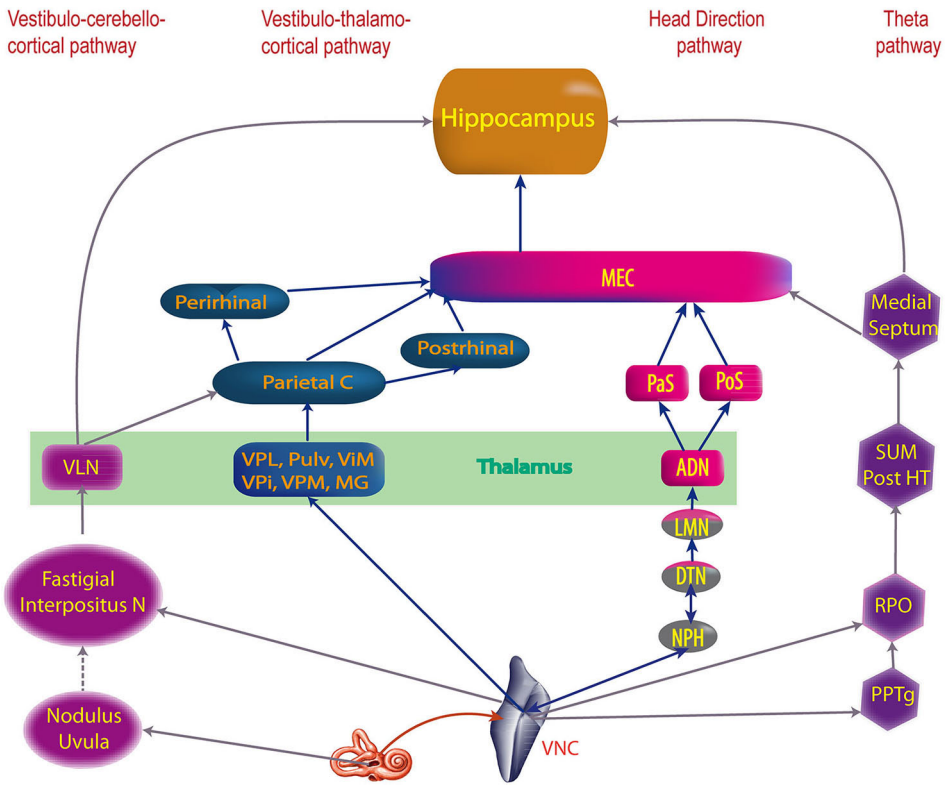


FIGURE 2 | The four main vestibular pathways to hippocampus. ADN, anterodorsal nucleus of the thalamus; DTN, dorsal tegmental nucleus; Interpositus N, anterior and posterior interposed nuclei; LMN, lateral mammillary nuclei; MEC, medial entorhinal cortex; MG, medial geniculate nucleus; NPH, nucleus prepositus hypoglossi; Parietal C, Parietal cortex; PaS, parasubiculum; Perirhinal, Perirhinal cortex; PoS, posterior subiculum (i.e dorsal part of the presubiculum); Post HT, posterior hypothalamus; Postrhinal, postrhinal cortex; PPTg, pedunculopontine tegmental nucleus; Pulv, pulvinar; RPO, reticularis pontis oralis; SUM, supramammillary nucleus; ViM, ventralis intermedius nuclei of the thalamus; VLN, ventral lateral nucleus of the thalamus; VNC, vestibular nucleus complex; VPi, ventral posterior inferior nucleus of the thalamus; VPL, ventral posterior lateral nucleus of the thalamus; VPM, ventral posterior medial nuclei of the thalamus (built from multiple references: cf text).

in the hippocampus. The formation of those maps probably depends on the grid cells and some integration of grid cell and HD firing in the entorhinal cortex (McNaughton et al., 2006; Fyhn et al., 2007; Brun et al., 2008; Moser et al., 2008; **Figure 2**). Activation of those maps depends on current location, environmental context, or current and recent environmental events (McNaughton et al., 1996; Sharp, 1999).

Besides the spatial representation integrated in these maps, place cells contribute to time representation of the past (spatial memory) and the future (navigational planning) (Leutgeb et al., 2005; Pfeiffer and Foster, 2013).

OTHER COGNITIVE PROCESSES INVOLVING VESTIBULAR INPUT

Beside spatial cognition, the vestibular system is also suspected to play a role in object recognition and possibly even numerical cognition.

Object recognition

Object recognition is impaired in rats, 3 and 6 months after bilateral vestibulectomy (Zheng et al., 2004). These results possibly arise from the loss of vestibular inputs in the entorhinal and perirhinal cortices. Those two cortical areas are indeed involved in object recognition (Mumby, 2001; Winters et al., 2004). Moreover, nitric oxide synthase—an enzyme involved in neuronal plasticity—decreases in the entorhinal and perirhinal cortices 2 weeks after unilateral vestibulectomy (Liu et al., 2004). Nevertheless object recognition was not impaired after sequential chemical vestibulectomy in rats, possibly as a result of partial compensation between the two lesions (Besnard et al., 2012).

The relation between vestibular stimulation and object recognition is probably integrated in place cells, as those cells are responsive to both spatial and non-spatial information, such as geometric and behavioral aspects of the environment (Brown and Taube, 2007).

Numerical cognition

The role of vestibular information in numerical tasks was first suspected clinically, after Risey and Briner (1990–1991) reported patients with vertigo who were having difficulties counting backwards by two. This result could be interpreted as an effect of vestibular dysfunction on spatial representation, which seems to play a role in number representation (see for review Smith, 2012).

The relation between numerosity and spatial representation is illustrated by self-motion direction influencing the processing of

numbers (Hartmann et al., 2012a). For instance, Hartmann et al. (2012b) showed that passive whole-body motion leftward and downward facilitated small number generation, whereas rightward and upward displacement facilitated the generation of large numbers. In addition, Lugli et al. (2013) showed that passive or active movement modulated the calculation process: addition was facilitated if moving up on an elevator, and subtraction when moving down.

The vestibular system may play a role in these processes, as galvanic vestibular stimulation also influences number generation (Ferrè et al., 2013). Finally, the parietal cortex and more particularly the ventro-intraparietal cortex is involved in number representation and is also one of the vestibular projection areas (Hubbard et al., 2005).

As the role of each of the vestibular cortical projection areas emerges and the integration of vestibular and other sensory information within the hippocampus is better understood, we need to specify the pathways that bring vestibular input to these areas. Most of them involve the thalamus; however, other pathways are possible.

Contrary to most sensory system pathways which reach one specific thalamic nucleus, vestibular input is distributed throughout more than 10 different nuclei (see Lopez and Blanke, 2011 for review).

FOUR PATHWAYS TO THE THALAMUS

Four pathways are known to transmit vestibular inputs to the thalamus: the medial longitudinal fasciculus, the ascending tract of Deiter, the crossing ventral tegmental tract and the ipsilateral vestibulo-thalamic tract (Zwergal et al., 2009). Except for the latter, all of these pathways are involved in vestibulo-ocular function. However, neurons involved in cognition (i.e., vestibular-only neurons) are different from those involved in vestibulo-ocular function (Cullen, 2012).

According to anatomical studies in monkeys, the medial longitudinal fasciculus links the vestibular nuclear complex (VNC) to the contralateral posterior thalamus (Lang et al., 1979; Zwergal et al., 2009). Additionally, studies in rats, cats and monkeys show an ipsilateral connection. Neuronal tracer studies demonstrate that the medial longitudinal fasciculus links: (1) the superior vestibular nucleus to the ipsilateral central lateral nucleus, bilateral ventro-postero-lateral and bilateral ventro-lateral thalamic nuclei; (2) the medial vestibular nucleus to the bilateral ventro-postero-lateral, and the contralateral central lateral thalamic nuclei; and (3) the descending vestibular nuclei to the contralateral medial geniculate nucleus (Lang et al., 1979; Kotchabhakdi et al., 1980; Nagata, 1986; Shiroyama et al., 1999). Moreover, pathologic lesions of the medial longitudinal fasciculus in humans have revealed alterations of the subjective visual vertical (i.e., capacity to orient vertically a bar in the dark) (Zwergal et al., 2008). Therefore, the medial longitudinal fasciculus is probably involved in the vestibular-perception network.

Compared to the medial longitudinal fasciculus, the ascending tract of Deiter links the superior vestibular nucleus and medial vestibular nucleus to the central-lateral, ventral-posterior-lateral and ventral-lateral thalamic nuclei in rats and cats (Kotchabhakdi et al., 1980; Maciewicz et al., 1982; Nagata, 1986; Shiroyama et al., 1999). In monkeys, few projections from the lateral part of the VNC reach the ipsilateral thalamus through the ascending tract of Deiter, the rostral ocular-motor nucleus and the H1 field of Forel (Zwergal et al., 2009). Nevertheless, if the ascending tract of Deiter is involved in oculomotor vergence, no role in vestibular cognition has been demonstrated yet (Zwergal et al., 2009).

Similarly, no cognitive role is proven for the crossing ventral tegmental tract. This vestibulo-oculomotor pathway transmits the anterior canal inputs through the superior vestibular nucleus and Y-group to the contralateral oculomotor nucleus (III), and also the thalamus (anatomical studies in monkey) (Lang et al., 1979; Zwergal et al., 2009).

The fourth vestibular pathway to the thalamus is the ipsilateral vestibulo-thalamic tract, which ascends from the Y-group and probably transmits otolithic signals to the postero-lateral thalamus (Zwergal et al., 2009). Clinical data in humans demonstrates the role of the ipsilateral vestibulo-thalamic tract in the subjective visual vertical; the ipsilateral vestibulo-thalamic tract is understood as a fast pathway transmitting vestibular information to the thalamus and vestibular cortices, which provides it to the cortical multisensory network for the perception of body motion and spatial orientation (Zwergal et al., 2009).

A fifth pathway may involve projections from the bilateral medial vestibular nuclei and the ipsilateral superior and descending vestibular nucleus, to the parafascicular nucleus (PFN) of the thalamus (Lai et al., 2000; see Lopez and Blanke, 2011, for a review). The central lateral and paracentral nuclei also receive vestibular inputs. Although it has not been demonstrated as yet, that the PFN and other intralaminar nuclei (ILN) neurons that receive vestibular input, project to the cortex, this is very likely since the ILN are known to have such projections (see Lopez and Blanke, 2011, for a review).

SYSTEMATIZATION BETWEEN THE VESTIBULAR NUCLEI, THALAMUS AND VESTIBULAR CORTICES

Every vestibular nucleus projects to several or many thalamic nuclei. Most of these projections are contralateral or bilateral (see for review Lopez and Blanke, 2011). Particularly the superior vestibular nucleus and the medial vestibular nucleus send projections to the thalamic ventral posterior complex: i.e., ventral-posterior-lateral nucleus, nucleus ventralis intermedius, ventral posterior medial nucleus or ventral posterior inferior nucleus (in certain species the difference between the ventral posterior medial nucleus and ventral posterior inferior nucleus is not clear) (see Lopez and Blanke, 2011 for review). The superior, medial, lateral and descending vestibular nuclei project to the medial geniculate, the lateral geniculate and the suprageniculate nuclei (Liedgren et al., 1976; Kotchabhakdi et al., 1980; Nagata, 1986; Shiroyama et al., 1999). However, Meng et al. (2007) found a much wider distribution of vestibular responses within the thalamus and reported evidence of cerebellar-thalamic projections which carry vestibular information.

Among the thalamic nuclei, some neurons are responsive only to vestibular stimulation (i.e., first order relay), for example, the ventral posterior complex (Marlinski and McCrea, 2008). Other vestibular thalamic nuclei are higher order relays which are also sensitive to somatosensory (e.g., ventral-posterior-lateral,

ventral-posterior-medial, ventral-posterior-inferior nuclei) or visual inputs (e.g., lateral geniculate nucleus) (Reichova and Sherman, 2004; Sherman, 2007; Sherman and Guillery, 2011). Vestibular thalamic nuclei project to primary somatosensory (area 3aV), visual (area 17) cortices and the polymodal parietal, temporal and insular cortices involved in spatial cognition (see Liedgren et al., 1976; Kotchabhakdi et al., 1980; Nagata, 1986; Akbarian et al., 1992; Reep et al., 1994; Shiroyama et al., 1999; Marlinski and McCrea, 2008; **Figure 3**). Some authors distinguish inside the ventroposterior thalamus a nucleus ventralis posterior superior (VPS) and a nucleus ventralis posterior pars posterior (VPP; Akbarian et al., 1992; Marlinski and McCrea, 2008). According to these authors, vestibular sensitive neurons from the VPS project to area 3aV, those from the VPP project to the PIVC and those from the oral and medial pulvinar to area T3.

The anatomical pathways from the thalamus to the cortices probably go through the three thalamic peduncles: the superior and posterior peduncles reaching the central parietal and occipital cortices; and the inferior thalamic peduncle, reaching the orbitofrontal, insular and temporal cortices (Nieuwenhuys et al., 2008).

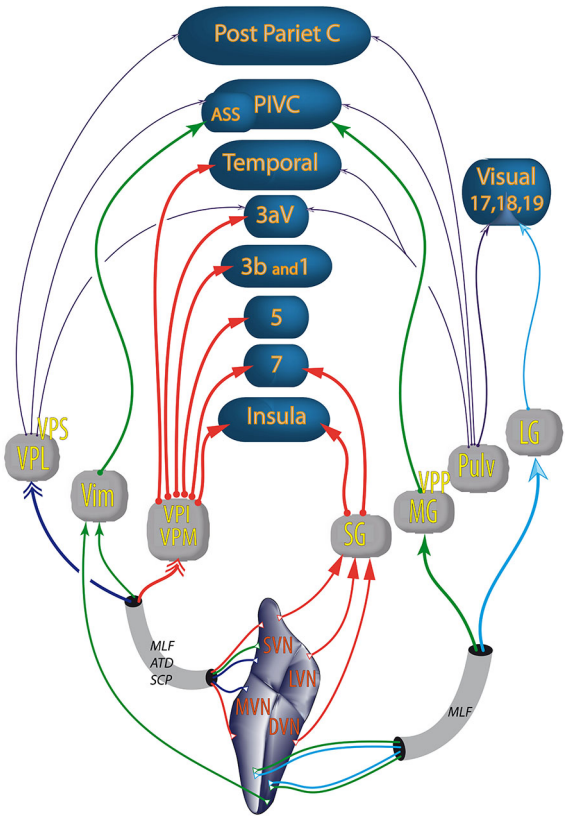


FIGURE 3 | Vestibular pathways to cortices through the thalamus. Colors of the arrows differentiate the thalamic nuclei. Double arrows (→>) correspond to bilateral projections. The other types and thickness of the arrows are varied to improve the readability of the figure; ATD, ascendant tractus of Deiters; ASS, anterior suprasylvian cortex (homolog in cats of the primate PIVC); DVN, descending vestibular nuclei; LG, lateral geniculate; LVN, lateral vestibular nuclei; MLF, medial longitudinal fasciculus; MG, medial geniculate nucleus; MVN, medial vestibular nuclei; PIVC, parieto insular vestibular cortex (in primates); Post Pariet C, posterior parietal cortex; Pulv, pulvinar; SG, suprageniculate nucleus; SCP, superior cerebellar pedunculus; SVN, superior vestibular nuclei; Temporal, temporal cortex; Vim, nucleus ventralis intermedius; VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior median nucleus; VPP, nucleus ventralis posterior pars posterior; VPS, ventral posterior superior nucleus; numbers (e.g., 5 or 3b) refer to Brodmann areas. From studies in rodents, cats and primates (Nagata, 1986; Akbarian et al., 1992; Reep et al., 1994; Marlinski and McCrea, 2008; Lopez and Blanke, 2011).

PATHWAY TO THE HIPPOCAMPUS

No direct projection from the VNC or thalamus to the hippocampus has ever been proven. Hence, the vestibular cortices are a good candidate to send vestibular inputs to the parahippocampal area (**Figure 4**). Most evidence concerns the posterior parietal cortex, including area 7a, which sends projections to the hippocampal CA1 area (anatomical studies in monkey) (Rockland and Van Hoesen, 1999). Additionally, another pathway, the "head direction pathway", reaches the hippocampus through the medial entorhinal cortex (MEC; Aggleton et al., 2000). The MEC contains place cells, grid cells and HD cells (see Taube, 2007; Moser et al., 2008 for reviews) and 16% of its inputs come from vestibular cortices involved in visuospatial function (i.e., posterior parietal cortex, cingulate and retrosplenial cortices). The parietal cortex itself represents 9% of the MEC's inputs. The posterior parietal cortex projects to the MEC, either directly or mostly through the postrhinal cortex (parahippocampal cortex in monkey) (Burwell and Amaral, 1998). Other indirect projections from the posterior parietal cortex to the MEC go through the perirhinal cortex (mostly area 36 rather than 35) or the PoS (Moser et al., 2008; Shinder and Taube, 2010 for reviews). However, these last two sources of inputs are minor compared with the postrhinal cortex,

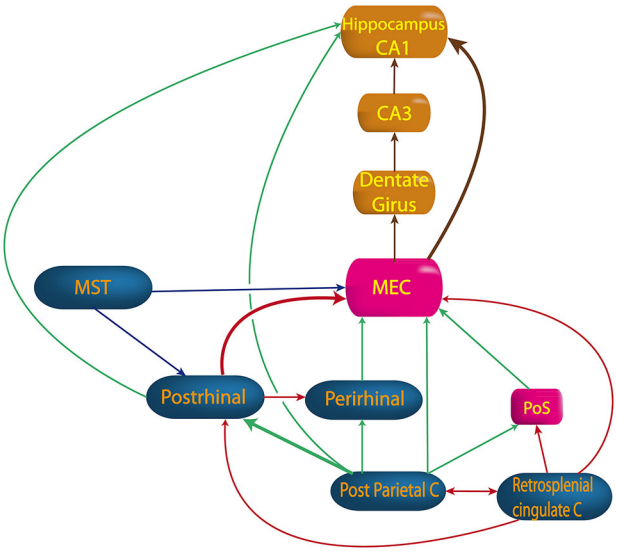


FIGURE 4 | Pathway from vestibular cortices to hippocampus. MEC, medial entorhinal cortex; MST, medial superior temporal cortex; Perirhinal, perirhinal cortex; PoS, posterior subiculum; Postrhinal, postrhinal cortex; Retrosplenial cingulate C, retrosplenial and cingulated cortices. (built from Burwell and Amaral, 1998; Rockland and Van Hoesen, 1999; Moser et al., 2008; Shinder and Taube, 2011).

in terms of their anatomical connections and their visuospatial functions (Burwell and Amaral, 1998; Aggleton et al., 2000). From the MEC (layer II), extensive projections reach the dentate gyrus then CA3 and CA1 (Burwell and Amaral, 1998; Brun et al., 2008). However, some direct connections also exist from the MEC (layer III) or from the postrhinal cortex to the hippocampus (Burwell and Amaral, 1998; see Moser et al., 2008 for review). These direct projections from layer III are more important for the accuracy of place fields in CA1 than the projections from layer II (Brun et al., 2008).

Other projections to the MEC come from the cingulate and the retrosplenial cortices, either directly or through the postrhinal cortex or the dorsal presubiculum (Burwell and Amaral, 1998; see Shinder and Taube, 2010 for review). Finally, projections also exist from the medial superior temporal area either directly or through the postrhinal cortex (see Shinder and Taube, 2010 for review).

The MEC seems to play a key role in spatial cognition as hippocampal place cells are related to entorhinal border cells, HD cells, and grid cells which determine place fields in the hippocampus (Brun et al., 2008; Zhang et al., 2013). However, abolition of the head direction signals in the antero-dorsal nucleus of the thalamus (ADN) and the dorsal presubiculum significantly degraded place cell responses in CA1 (Calton et al., 2003), suggesting that the vestibulo-thalamo-cortical pathway may not be independent of the head direction pathway.

THE PATHWAY FROM THE DORSAL TEGMENTAL NUCLEUS TO THE ENTORHINAL CORTEX

Beside a representation of position (place cells), a representation of direction (HD cells) is essential to navigate without landmarks (e.g., an unknown environment) (see Etienne and Jeffery, 2004 for review). Vestibular inputs are fundamental to head direction representation, especially when visual cues are absent (e.g., in darkness or in a desert) (Blair and Sharp, 1996). Consequently, the HD cell signal is abolished in the ADN after bilateral vestibulectomy by arsanilate, and also in the PoS after intratympanic injection of tetrodotoxin (Stackman and Taube, 1997; Stackman et al., 2002). Vestibular input is fundamental as the HD signal does not recover even 3 months after the lesion, showing that other sensory inputs are not sufficient to compensate for the loss of vestibular signals (Clark and Taube, 2012). Both semicircular canals and otoliths play a role as the HD signal is disrupted after canal occlusion (Muir et al., 2009) and is unstable in otolithic deficient mice (Beraneck and Lambert, 2009; Yoder and Taube, 2009).

LOCATION OF THE HD SIGNAL

Although HD cells were first described in the PoS (Ranck, 1984; Taube et al., 1990), they have been found since in all the areas of the limbic system: the lateral mammillary nuclei (Stackman and Taube, 1998), anterior dorsal thalamic nucleus (Taube and Burton, 1995), retrosplenial cortex (Chen et al., 1994), entorhinal cortex (Sargolini et al., 2006) and CA1 (Leutgeb et al., 2000). However, they are also found in non-limbic areas, such as the dorsal tegmental nucleus, the lateral dorsal thalamus (Mizumori and Williams, 1993), the dorsal striatum (Wiener, 1993; Mizumori et al., 2000), the medial prefrontal cortex (i.e., FR2 or AGm cortex) (Taube, 2007), and the medial prestriate cortex (Chen et al., 1994).

The concentration of HD cells in each of these areas varies from 60% of the cells in the ADN (Taube and Burton, 1995), 30% in the lateral dorsal thalamus (Mizumori and Williams, 1993), 25% in the PoS and lateral mammillary nucleus, 12% in the dorsal tegmental nucleus (Sharp et al., 2001), 10% in the retrosplenial cortex to 6% in the striatum (Mizumori et al., 2000).

ANGULAR HEAD VELOCITY CELLS

In addition to the classical HD cells, some cells fire in relation to the speed and direction when an animal turns its head. These "Angular Head Velocity" cells (AHV) are found mostly in the dorsal tegmental nucleus (75% of the cells) (Bassett and Taube, 2001), in the lateral mammillary nucleus (50% of the cells) (Stackman and Taube, 1998) and also in the lateral habenula (Taube, 2007).

ORGANIZATION OF THE HD PATHWAY

Several lesion studies have deduced the pathways connecting areas with HD cells (**Figure 5**). Bilateral lesions of vestibular labyrinth, the dorsal tegmental nucleus or the lateral mammillary nucleus disrupt the HD signal in the ADN (Stackman and Taube, 1997; Blair et al., 1998; Bassett et al., 2007). Additionally, lesions of the ADN or the lateral mammillary nucleus disrupt the HD signal in the PoS, the MEC and the parasubiculum (Goodridge and Taube, 1997; Blair et al., 1998; Bassett et al., 2007; Sharp and Koester, 2008; Clark and Taube, 2012).

However, the HD signal in the ADN is not disrupted by lesions of the PoS, nor lesions of the hippocampus, the retrosplenial cortex, the parietal cortex, or the MEC (Golob and Taube, 1997; Calton et al., 2008; Clark et al., 2010; Clark and Taube, 2012); and lesions of the parietal cortex do not disrupt the HD signal in the MEC (Clark and Taube, 2012); lesions in the hippocampus do not disrupt the HD signal in the PoS (Golob and Taube, 1997, 1999) and lesions in the PoS do not disrupt the HD signal in the lateral mammillary nucleus (Clark and Taube, 2012).

All of these results suggest that the HD signal from the vestibular nuclei is transmitted to the dorsal tegmental nucleus, then the lateral mammillary nucleus, the ADN and finally the PoS, parasubiculum and MEC. Nevertheless, no direct anatomical pathways are described to explain the transmission of vestibular input to the dorsal tegmental nucleus (Taube, 2007). However, indirect pathways are known through the nucleus prepositus hypoglossi or the supragenual nucleus (Liu et al., 1984; McCrea and Baker, 1985; Graf et al., 2002; Biazoli et al., 2006). No HD nor AHV cells are described in these nuclei, but the prepositus hypoglossi prolongs the phase of the vestibular signals (beyond 90° relative to velocity) compared to the signal in the vestibular nerve i.e., "mathematical integration" towards 180° out of phase with velocity (Taube, 2007). This could play a role in the HD signal generation. Besides, the supragenual nucleus seems essential for the HD signal as bilateral lesions of it significantly reduce the number of HD cells in the ADN (Clark et al., 2012; **Figure 6**).

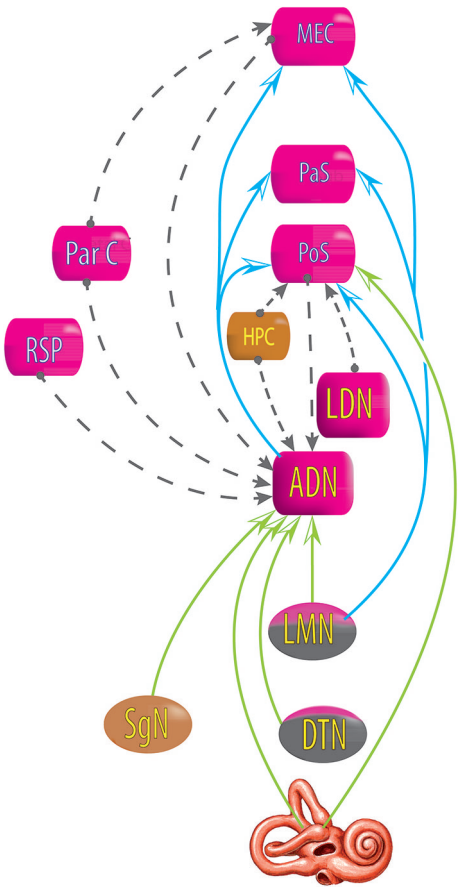


FIGURE 5 | Relationship between areas exhibiting head direction signals, deduced from lesion studies. Blue and green arrows: lesions at the starting area disrupt the head direction signal in the end area. Gray dashed line arrows: lesions at the starting area do not disrupt head direction signal in the end area. DTN, dorsal tegmental nucleus; LMN, lateral mammillary nucleus; AND, antero dorsal nucleus of the thalamus; LDN, latero dorsal thalamus; HPC, hippocampus; PoS, posterior subiculum; RSP, retrosplenial cortex; ParC, partietal cortex; PaS, parasubiculum; MEC, medial entorhinal cortex (see review in Clark and Taube, 2012).

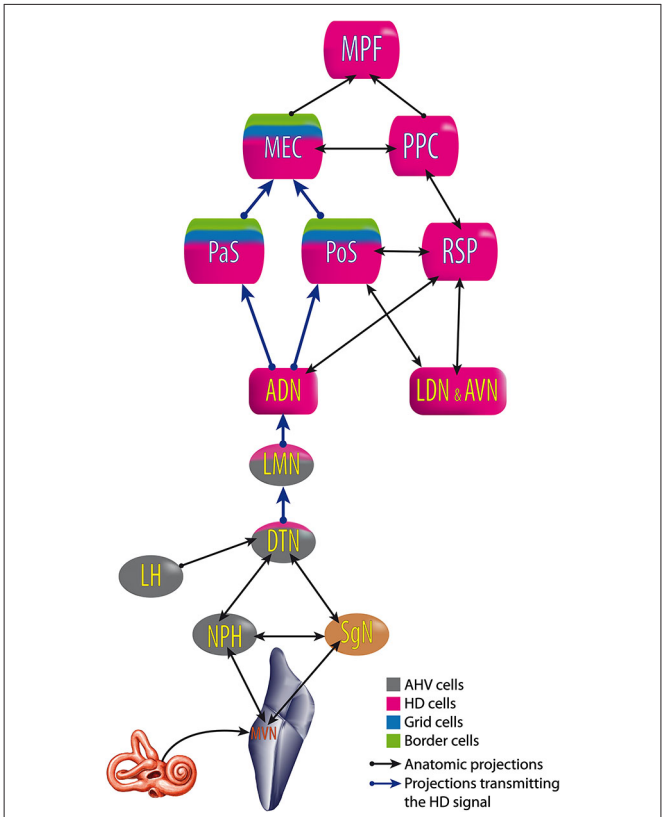


FIGURE 6 | Head Direction pathway. ADN, anterodorsal thalamus; AVN, anteroventral thalamus; DTN, dorsal tegmental nucleus; LDN, laterodorsal thalamus; LMN, lateral mammillary nuclei; MEC, medial entorhinal cortex; MPF, medial prefrontal cortex; MVN, medial vestibular nuclei; NPH, nucleus prepositus hypoglossi; PaS, parasubiculum; PoS, postsubiculum; PPC, posterior parietal cortex; RSP, retrosplenial cortex; SgN, supragenual nucleus. Built from Hoover and Vertes (2007); Taube (2007) and Clark and Taube (2012).

THE PATHWAY FROM THE NUCLEUS RETICULARIS PONTIS ORALIS, TO THE MEDIAL SEPTUM TO THE HIPPOCAMPUS

Hippocampal theta rhythm (theta) is an oscillating electrical signal within the 4–10 Hz frequency range found in rodents (rabbit, mice, rat), but also dogs and cats. Theta at this frequency is almost absent in monkeys, and rare or absent in humans (Niedermeyer, 2008) but the equivalent of theta in humans could be in fact much slower (1–4 Hz) (Jacobs, 2014). Theta rhythm can be found in the dentate gyrus and CA1 of the hippocampus, but also in the subiculum, the entorhinal cortex, the cingulate cortex, the mammillary bodies, the posterior hypothalamus, the amygdala and the prefrontal cortex (O'Keefe, 1993; Niedermeyer, 2008; Hartley et al., 2014).

Cognitive functions like spatial orientation or spatial memory require theta rhythm in the hippocampus (Leutgeb et al., 2005), probably because theta establishes a subthreshold membrane potential and modulates the spiking activity of hippocampal, entorhinal, and septal neurons endowed with voltage-dependent channels (Leung and Yim, 1986; Vertes and Kocsis, 1997; Buzsáki, 2002; Lubenov and Siapas, 2009).

INFLUENCE OF VESTIBULAR INPUT ON THETA

Several authors have argued that vestibular input can influence theta rhythm. For instance, passive rotation of awake restrained rats increases theta power in both light and complete darkness and this increase appeared with vestibular nystagmus (Gavrilov et al., 1995, 1996). Theta power also increases during passive translation in rats but less so during rotation (Gavrilov et al., 1996). More precisely, the theta rhythm induced by rotation is sensitive to atropine (Type 2 Theta) (Shin, 2010) and most probably linked to the cholinergic neurons of the medial septum (Tai et al., 2012). In cats and dogs, passive translation does not increase the power but increases the peak frequency of theta (Arnolds et al., 1984). Moreover, vestibular lesions decrease the power and the frequency of theta (Russell et al., 2006; Neo et al., 2012; Tai et al., 2012). Nevertheless, restoration of theta in vestibular-deficient rats, by medial septum stimulation, is not sufficient to compensate for

cognitive impairment induced by vestibular lesions (Neo et al., 2012).

THETA PATHWAY

Structures involved in theta rhythm include the reticularis pontis oralis, the pedonculopontine tegmental nucleus (PPTg), the supramammillary nucleus, the posterior hypothalamus, the septal complex, the entorhinal cortex and the hippocampus (Vertes and Kocsis, 1997; Bland and Oddie, 1998; Pignatelli et al., 2012).

During theta, ascending signals from the reticularis pontis oralis activate neurons of the supramammillary nucleus; the supramammillary nucleus, in turn, converts this steady barrage of action potentials into a rhythmical pattern of discharge which is relayed to GABAergic/cholinergic rhythmically-bursting cells of the medial septum. The septal rhythmically bursting cells modulate subsets of hippocampal interneurons and principal cells in the generation of theta rhythm (see for review Vertes and Kocsis, 1997). A reduction of theta oscillation in the medial septum has been reported to disrupt the spatial selectivity of grid cells but not place cells or HD cells (Brandon et al., 2011; Koenig et al., 2011).

In this system the PPTg appears to modulate the reticularis pontis oralis activity through direct cholinergic projections (Shiromani et al., 1988; Semba and Fibiger, 1992; Vertes and Kocsis, 1997). Vestibular inputs are known to project to both the PPTg and reticularis pontis oralis (Vertes and Kocsis, 1997; Bland and Oddie, 1998; Seemungal et al., 2010; Aravamuthan and Angelaki, 2012). The influence of the vestibular system seems important as 72.5% of the PPTg's neurons in monkeys respond to vestibular stimulation (rotation or translation) (Aravamuthan and Angelaki, 2012).

Besides the PPTg, the vestibular system could influence theta rhythm through the ventral tegmental nucleus of Gudden. This pontic nucleus generates a bursting rhythmic activity that precedes theta activity in the hippocampus (Bassant and Poindessous-Jazat, 2001). Moreover, the ventral tegmental nucleus projects extensively to the median mammillary body involved in the limbic system. Consequently, lesions of the ventral tegmental nucleus impair spatial learning and memory in rats and humans (Vann, 2009). The role of vestibular input in this system has never been studied, but the medial, lateral and superior vestibular nuclei project to the ventral tegmental nucleus, as shown by neuronal tracer studies in mice, rats and cats (Irle et al., 1984). Theta rhythm is also found in the cerebellum (lobule HVI and interposed nucleus) where it is synchronized with hippocampal theta (Hoffmann and Berry, 2009; Wikgren et al., 2010). This phenomenon is thought to enhance associative learning abilities (Hoffmann and Berry, 2009).

A POSSIBLE PATHWAY VIA THE CEREBELLUM TO THE PARIETAL CORTEX?

ROLE OF THE CEREBELLUM IN SPATIAL ORIENTATION

The role of the cerebellum in spatial orientation is evident in both humans and animals (see for review Rochefort et al., 2013). The cerebellum is activated on fMRI during virtual navigation (Moffat et al., 2006); and patients with cerebellar lesions suffer from visuospatial, linguistic and affective impairment known as the Cerebellar Cognitive Affective Syndrome (Schmahmann and Sherman, 1998; Middleton and Strick, 2000; Schmahmann, 2001; Partridge et al., 2010). According to clinical cases, the visuospatial function could be located in the nucleus dentate and cerebellar hemispheres (Schmahmann, 1996, 2004).

Other proof of cerebellar involvement in cognition comes from several types of cerebellar mutant mice showing impaired spatial learning, especially if Purkinje cells are deficient (Mullen et al., 1976; Goodlett et al., 1992; Hilber et al., 1998; Rondi-Reig and Burguière, 2005). Additionally, rats with lesions of the pontine nuclei-granule cell-parallel pathway—which transmits vestibular input to the cerebellar cortex—fail to learn the spatial task of the non-visual water-maze, contrary to rats with lesions of the climbing fibers (Rondi-Reig et al., 2002; Barmack, 2003).

Finally, vestibular input reaching the nodulus (cerebellum lobule 10) and uvula (lobule 9) changes from an egocentric representation to an allocentric representation in the Purkinje cells recorded in monkeys (Yakusheva et al., 2007; Angelaki et al., 2010). The rostral fastigial nucleus, on the other hand, integrates vestibular and proprioceptive input to integrate body motion in an egocentric head-centered-reference frame and vestibular signals from a head- to a body-centered-reference frame (Brooks and Cullen, 2009).

CONNECTIONS FROM THE VESTIBULAR SYSTEM TO THE CEREBELLUM

The cerebellum receives direct projections from the vestibular nerve, bypassing the VNC. Most of these projections (>70%) terminate in the nodulus and uvula as mossy fibers (Korte and Mugnaini, 1979; Angelaki et al., 2010). Other vestibular projections come from the VNC (i.e., the superior, medial and descending nuclei, group Y). The VNC projects bilaterally to the flocculus, the fastigial nucleus, the anterior and posterior interposed nuclei and the posterior vermis (mostly the uvula (lobule 9), but also the declive, folium, tuber, and pyramide (lobules 6, 7 and 8)) (Carpenter et al., 1972; Kotchabhakdi and Walberg, 1978; Blanks et al., 1983; Brodal and Brodal, 1985; Walberg and Dietrichs, 1988; Thunnissen et al., 1989; Epema et al., 1990).

CONNECTIONS FROM THE CEREBELLUM TO THE HIPPOCAMPUS

Direct connections from the cerebellum to the hippocampus are suspected, as stimulation of the rostral vermis, fastigial nucleus, and intervening midline folia of the cerebellum, inhibit hippocampal activity with a short latency (Maiti and Snider, 1975; Heath et al., 1978; Newman and Reza, 1979).

Additionally, lesions of the fastigial nucleus induce bilateral degeneration in the hippocampal formation, including CA2, CA3, dentate gyrus and subiculum. Any pathway from the cerebellum to the hippocampus seems likely to go through the fimbria or the dorsal fornix, presubiculum and subiculum (Heath and Harper, 1974).

No direct connections are known between the nodulus or uvula and the hippocampus, but indirect connections are hypothesized (e.g., through the fastigial nucleus) (Yakusheva et al., 2013).

CONNECTIONS FROM THE CEREBELLUM THROUGH THE THALAMUS

Vestibular input from the fastigial, dentate and interposed nuclei project to the thalamus, mostly in the ventro-lateral nucleus (VLN), but also the ventro-postero-lateral and the medio-dorsal

nucleus (paralamellar portion) (Haroian et al., 1981; Angaut et al., 1985; Aumann et al., 1994). The VLN receives vestibular input from the cerebellum in monkeys and both the cerebellum and VNC in rats and cats (Kotchabhakdi et al., 1980; Maciewicz et al., 1982; Nagata, 1986; Shiroyama et al., 1999; Meng et al., 2007).

Anatomical studies show connections from the VLN to three parietal vestibular cortices involved in cognition: the area 3aV, the area 2v (Morecraft et al., 1993) and the posterior parietal cortex (Amino et al., 2001). Moreover, electrical stimulation of the dentate, interposed or fastigial nuclei induces field potentials in the posterior parietal cortex of monkeys, demonstrating a functional link between the cerebellum and the vestibular cortex (Amino et al., 2001).

NEW HYPOTHETICAL PATHWAY TO THE BASAL GANGLIA

ROLE OF THE BASAL GANGLIA IN SPATIAL COGNITION

Besides the hippocampus, growing evidence suggests the basal ganglia as a key center for spatial cognition (for review see Mizumori et al., 2009; Retailleau et al., 2012).

The ventral striatum (nucleus accumbens) is involved in both short-term spatial learning and long-term spatial memory as demonstrated by inhibiting striatal glutamate receptors (NMDA and AMPA), or interfering with transcription factors (i.e., CREB) or protein synthesis (Atallah et al., 2006; Ferretti et al., 2007, 2010). Moreover, behavioral studies demonstrate an allocentric spatial representation in the ventral striatum and the postero-dorsomedial striatum, compared with egocentric representation in the dorso-lateral striatum which contains HD cells (Wiener, 1993; Ferretti et al., 2007; Retailleau et al., 2012).

ROLE OF VESTIBULAR INPUT IN THE COGNITIVE FUNCTIONS OF THE BASAL GANGLIA

Since the early 1970's, electrophysiological studies have demonstrated responses in the caudate nucleus in response to electrical stimulation of the vestibular nerve (Potegal et al., 1971; Liedgren et al., 1976; cats and squirrel monkeys) or vestibular nucleus (Spiegel et al., 1965; cats). Field potential responses were also obtained in the putamen (Spiegel et al., 1965; Liedgren et al., 1976). However, in alert rhesus monkeys, Matsunami and Cohen (1975) could obtain responses only in the caudate nucleus and globus pallidus at stimulus amplitudes that evoked body movement and therefore it was unclear whether the response was to vestibular stimulation itself. Other evidence for a vestibular-striatal connection comes from vestibular-deficient mutant mice which exhibit an increase in pCREB—a protein involved in spatial memory consolidation—specifically in the striatum (Ferretti et al., 2010; Antoine et al., 2013). Moreover, an anatomical pathway has been demonstrated between the medial vestibular nucleus and the dorsolateral striatum in rats, going through the parafascicular thalamic nucleus (Nagata, 1986; Shiroyama et al., 1999; Lai et al., 2000).

STRIATUM-HIPPOCAMPUS CONNECTIONS

The striatum is interconnected with the hippocampus (Scatton et al., 1980; Gasbarri et al., 1994; Floresco et al., 2001; van der Meer et al., 2010). The spatial representation in these two areas is used to perform different types of navigation based on either procedural memory for the striatum, or declarative memory for the hippocampus. Vestibular input influences the strategy of navigation, as rats with bilateral vestibulectomy use a procedural response compared with controls which use procedural and declarative memory-based navigation equally (Machado et al., 2014).

CONCLUSION

The knowledge of the anatomical bases of vestibular contributions to cognition has significantly increased in the past decade, suggesting four pathways and perhaps a fifth one through the striatum. Particularly the role of vestibular input in the pathway from the dorsal tegmental nucleus via the lateral mammillary nucleus, the anterodorsal nucleus of the thalamus to the entorhinal cortex, is better understood as well as the organization of the nuclei along this pathway. Nevertheless, some major questions remain such as how and where is the HD signal processed, why do HD cells exist in so many brain areas and what role do they play in each area? The lack of specific cells, such as HD cells, along the other pathways make them more difficult to study and the role of each pathway more difficult to identify. Moreover, several pathways probably interact with each other. For example, the suppression of the HD signal does not suppress the place cell signal in the hippocampus (independent pathways) but significantly degrades it (interaction of the pathways) (Calton et al., 2003). All of the pathways may also interact in the different vestibular cortices or in the hippocampal formation and some of them in the thalamus as well.

Another level of complexity occurs as vestibular inputs are integrated with other sensory inputs in the VNC, which makes them more difficult to isolate. Additionally, the complexity increases as the vestibular signals are disseminated throughout the four pathways described, but also within some pathways (before the thalamus for example in the vestibulo-thalamo-cortical pathway). This wide dissemination of vestibular signals could result from an evolutionary process to elaborate a neural network with sparse coding (Olshausen and Field, 2004; Niven and Laughlin, 2008). Indeed sparse coding is thought to provide a sensory system network at a low energy cost, with a large storage capacity, rapid learning ability, and tolerance to degradation of the network or noise in the input (Olshausen and Field, 2004; Waydo et al., 2006; Quiroga et al., 2008).

To address this complexity, research in vestibular cognition could benefit from new techniques in anatomy (Chung et al., 2013), in electrophysiology (e.g., optogenetic methods), new behavioral tests able to discriminate different cognitive strategies and improvements in functional imaging. Those efforts will increase the probability of better understanding how the vestibular system evolved, what role it plays in cognitive function and how vestibular pathology can impair cognitive functions. Do these cognitive impairments compensate, and how can we treat them?

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Vestibular control of entorhinal cortex activity in spatial navigation

Pierre-Yves Jacob [1], ***Bruno Poucet*** [1], ***Martine Liberge*** [1], ***Etienne Save*** [1] ***and Francesca Sargolini*** [1,2]*

[1] *Laboratoire de Neurosciences Cognitives UMR7291, Fédération 3C FR3512, Université d'Aix-Marseille - CNRS, Marseille, France*
[2] *Institut Universitaire de France, Paris, France*

Edited by:
Stephane Besnard, INSERM U1075, France

Reviewed by:
David Clayton Rowland, Norwegian University of Science and Technology, Norway
Paul Smith, University of Otago Medical School, New Zealand

***Correspondence:**
Francesca Sargolini, Laboratoire de Neurosciences Cognitives UMR7291, Fédération 3C (Case C), Aix Marseille Université - CNRS, 3 Place Victor Hugo, 13331 Marseille, Cedex 3, France
e-mail:
francesca.sargolini@univ-amu.fr

Navigation in rodents depends on both self-motion (idiothetic) and external (allothetic) information. Idiothetic information has a predominant role when allothetic information is absent or irrelevant. The vestibular system is a major source of idiothetic information in mammals. By integrating the signals generated by angular and linear accelerations during exploration, a rat is able to generate and update a vector pointing to its starting place and to perform accurate return. This navigation strategy, called path integration, has been shown to involve a network of brain structures. Among these structures, the entorhinal cortex (EC) may play a pivotal role as suggested by lesion and electrophysiological data. In particular, it has been recently discovered that some neurons in the medial EC display multiple firing fields producing a regular grid-like pattern across the environment. Such regular activity may arise from the integration of idiothetic information. This hypothesis would be strongly strengthened if it was shown that manipulation of vestibular information interferes with grid cell activity. In the present paper we review neuroanatomical and functional evidence indicating that the vestibular system influences the activity of the brain network involved in spatial navigation. We also provide new data on the effects of reversible inactivation of the peripheral vestibular system on the EC theta rhythm. The main result is that tetrodotoxin (TTX) administration abolishes velocity-controlled theta oscillations in the EC, indicating that vestibular information is necessary for EC activity. Since recent data demonstrate that disruption of theta rhythm in the medial EC induces a disorganization of grid cell firing, our findings indicate that the integration of idiothetic information in the EC is essential to form a spatial representation of the environment.

Keywords: path integration, vestibular system, entorhinal cortex, grid cells, theta rhythm, rat

VESTIBULAR SYSTEM AND SPATIAL NAVIGATION

To successfully navigate in their environment, humans and other animals can rely on two types of sensory cues, allothetic cues (environmental, e.g., visual, olfactory and auditory) and idiothetic cues (self-motion, e.g., vestibular, somatosensory information, motor efference copy, and optic flow). Because in a cue-rich environment animals may use both types of cues, the importance of idiothetic cues in navigation is mostly revealed through the ability of mammals to navigate without help of any external references (Etienne et al., 1996; Etienne and Jeffery, 2004). Thus, in the absence of relevant visual information (e.g., in darkness) or familiar landmarks, idiothetic cues support a form of navigation called path integration. An animal that performs path integration in darkness is, in principle, able to return by a straight path to its departure point after a sinuous journey through the environment. It is assumed that along its journey, the animal computes and continuously updates a return (or homing) vector pointing to the departure point by measuring and integrating angular and linear self-motion accelerations (Mittlestaedt and Mittlestaedt, 1982; Benhamou, 1997). Path integration involves multiple motor and sensory cues, and therefore necessarily involves multiple brain regions. Over the last two decades, data have accumulated showing that path integration involves a large network of brain areas including cortical and subcortical structures (Etienne and Jeffery, 2004). But how idiothetic cues are conveyed and processed by these structures and how they contribute to spatial navigation remains unclear.

The vestibular system is a major source of idiothetic information in mammals. The vestibular apparatus detects both angular and linear accelerations of the head, and these signals are conveyed to the central vestibular nuclei (VNC) to build a neuronal representation of angular and linear head velocity. Damage to the peripheral vestibular system in the rat produces deficits in a large variety of spatial tasks, including navigation tasks based on idiothetic (Wallace et al., 2002; Zheng et al., 2009) or allothetic information (Semenov and Bures, 1989; Ossenkopp and Hargreaves, 1993; Stackman and Herbert, 2002; Baek et al., 2010), and object recognition tasks (Zheng et al., 2004; Besnard et al., 2012; reviews in Smith, 1997 and Smith et al. 2010). These data indicate that the vestibular signal influences several aspects of spatial cognition, thus implicating a functional interaction between the vestibular system and the brain network involved in spatial

information processing and navigation. Both neuroanatomical and lesion studies support this hypothesis.

There are multiple ascending pathways that convey the vestibular signal to the cerebral cortical centers involved in spatial cognition, and particularly the hippocampal formation and the entorhinal cortex (EC; **Figure 1**; reviews, Smith, 1997; Smith et al., 2005; Shinder and Taube, 2010). The outputs from the VNC are conveyed by vestibulo-cortical pathways via the thalamus nuclei, i.e., lateral posterior, ventral posterior, medial geniculate, and ventrolateral geniculate nuclei, to several cortical regions including the visual and parietal cortices (Brotchie et al., 1995; Stackman et al., 2002). In addition, the vestibulo-cerebellar-cortical pathway conveys vestibular information to the parietal and retrosplenial cortices, which in turn project to the hippocampus through the EC (Amino et al., 2001 for a review see also Voogd et al., 1996). In this regard, it is interesting to note that the cerebellum influences hippocampal place cell activity when only self motion is used, e.g., in the dark (Rochefort et al., 2011). An important pathway involves the head-direction cell system, a network containing cells that are characterized by head direction-specific firing. The VNC fibers contact the dorsal tegmental nucleus which projects to the lateral mammillary nucleus, then to the anterodorsal thalamic nucleus and the postsubiculum, two structures that contain sharply tuned head-direction cells (Taube, 2007). This network eventually provides an input to the EC and to the hippocampus (Robertson and Kaitz, 1981; Witter et al., 1988; for a review see Amaral and Witter, 1989). Finally, it has been suggested that vestibular information reaches the hippocampus and the EC via the theta-generating system that involves the pedunculopontine tegmental nucleus, the supramammillary nucleus and the medial septum (Smith et al., 2005). Overall, the entorhinal-hippocampal system receives a large amount of highly processed vestibular information which may be essential for spatial information processing and navigation. Consistent with this hypothesis, several studies have shown that the vestibular signal has a strong impact on the activity of the different categories of spatially-selective cells. These neurons include the hippocampal place cells (O'Keefe and Dostrovsky, 1971), that fire when the animal moves through a particular location in space, and the head-direction cells in the dorsal presubiculum (or post-subiculum) (Rank, 1984) and the antero-dorsal thalamus (Taube, 1995), whose activity is controlled by the position of the head in space. Direct or indirect stimulation of the vestibular apparatus influences place cell activity. For exemple, Horii et al. (2004) showed that electrical stimulation of the VNC increased the firing rates of CA1 cells, in anesthetized rats. Similarly, Sharp et al. (1995) observed that indirect stimulation of the vestibular system through maze rotations strongly influenced the spatial properties of the hippocampal place cells. In addition, temporary and permanent inactivation of the peripheral vestibular system affects theta oscillations in the hippocampus (Russell et al., 2006) and disrupts location-specific firing of place cells (Stackman et al., 2002; Russell et al., 2003). Similarly, the direction-specific firing of head direction cells in the postsubiculum and the anterior thalamus is strongly altered following vestibular dysfunctions (Stackman and Taube, 1997; Stackman et al., 2002; Muir et al., 2009; Yoder and Taube, 2009). These results are in accordance with early studies showing that the firing properties of place cells and head-direction cells are influenced by idiothetic cues (Muller and Kubie, 1987; Wiener et al., 1995; Gothard et al., 1996; Rotenberg and Muller, 1997; Knierim et al., 1998; Save et al., 1998, 2000). Moreover, they demonstrate a major role of the vestibular system in controlling the firing properties of cells located in a brain network whose activity strongly supports spatial navigation.

Spatial signals are not exclusive to the hippocampal formation. Recent studies have shown that the EC, a major source of afferent input for the hippocampus (Steward and Scoville, 1976; Köhler, 1985; for a review see Amaral and Witter, 1989), contains both

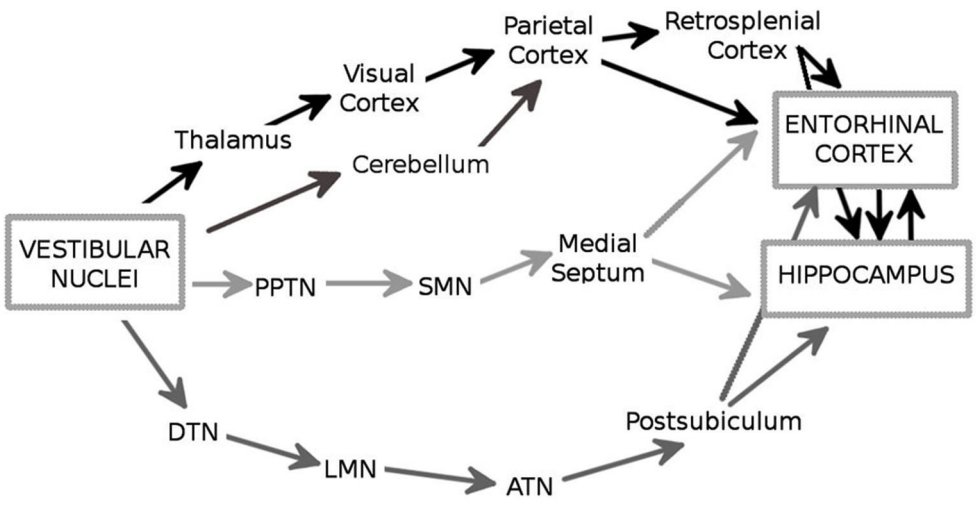


FIGURE 1 | The major anatomical pathways (in black, dark gray and light gray) through which the vestibular signals reach the hippocampus and the entorhinal cortex (EC).

PPTN: pedunculopontine nucleus; SMN: supramammilary nucleus; DTN: dorsal tegmental nucleus; LMN: lateral mammilary nucleus; ATN: anterodorsal thalamic nucleus.

position-selective cells and head-direction cells (Fyhn et al., 2004; Hafting et al., 2005; Sargolini et al., 2006). The activity of this cell network is supposed to underlie self-motion based navigation. This hypothesis is supported by both lesion studies showing that damage extended to the entire EC or restricted to the medial portion impairs path integration in a homing task (Parron and Save, 2004; Van Cauter et al., 2013), and electrophysiological data showing the existence of spatially-selective cells in the same area. This last issue is further developed in the next paragraph.

ENTORHINAL GRID CELLS AS A MAJOR SUPPORT FOR NAVIGATION GUIDED BY SELF-MOTION CUES

Exploration of single cell spatial firing properties in the EC was initially motivated by the high density of inputs from the EC to the hippocampus. Following an initial report by Quirk et al. (1992) who recorded from the most ventral region, studies of the spatial firing properties in the EC culminated in the discovery of "grid cells" in the most dorsal region (Fyhn et al., 2004; Hafting et al., 2005). Grid cells share with place cells a form of location-specific firing but differ in that they are characterized by multiple firing fields arranged in a remarkably regular lattice of equilateral triangles (or regular hexagons). The activity of a given grid cell can be described with three parameters, namely, the scale, the orientation and spatial phase (**Figure 2**). Scale is represented by the field spacing, i.e., the distance between two vertices of the smallest triangle. Orientation can be taken as the angle in the range $\pm 30°$ between horizontal and the closest triangle leg. Spatial phase is the location of a single reference field (**Figure 2**). Neighboring grid cells have similar orientation and scale but their spatial phases are distributed so as to cover the entire apparatus. The scale of the grid increases progressively as one gets more ventrally in the EC, and this property seems to depend upon the intrinsic oscillatory characteristics of the cells located at different levels along the dorso-ventral axis (Giocomo et al., 2007). The combination of grids at variable scales either within the EC or downstream in the hippocampus potentially provides a high resolution spatial coordinated system for navigation over large space. Grid cells are found mainly in layer II of the dorsal medial entorhinal cortex (dMEC), which projects to the dentate gyrus and CA3. In all other layers, grid cells coexist with head-direction cells and "conjunctive cells", so named because their activity depends on head direction as well as location (Sargolini et al., 2006; Boccara et al., 2010), and border cells (Solstad et al., 2008). Altogether these cells may provide a conjunctive representation of position and direction as well as landmark-related information, thus providing a continuous update of the rat's localization by self-motion cues and at the same time preventing cumulative drift during path integration.

The relative angles and densities of the vertices within grids of neighboring cells remain invariant both across environments and in response to changes in environmental cues. For example, changing the geometry of the environment (square vs. circle) does not alter the metric properties of the grid cell map in a stable manner: the scale and orientation of the map remain constant, whereas the spatial phase shifts randomly (Fyhn et al., 2007). Moreover, the grid map is stable in the absence of external landmarks (for example in the dark) (Hafting et al., 2005). Altogether these results indicate a strong dependence of grid cell activity on idiothetic cues. In essence, the metric organization of grid cell firing fields provides a directionally oriented, topographically organized neural map of the environment and the varying grid scale permits path integration calculations based on self-motion information (McNaughton et al., 2006). Recent studies however raise the question of whether such striking triangular organization is exclusively dependent on self-motion cues. When animals are exposed to a novel environment the grid map tends to expand (i.e., field spacing increases) (Barry et al., 2012; Stensola et al., 2012). A similar effect was observed following modification of the geometry of the environment (Barry et al., 2007). However, in both cases the grid map reverts to the original metric configuration following repeated exploration of the same environment, thus pleading in favor of the existence of an invariant self-motion-based spatial map (Jeffery and Burgess, 2006; Moser and Moser, 2008). It is presently unknown whether the grid cells provide such an invariant map and how external cues specifically influence their firing properties (Poucet et al., 2014). However there

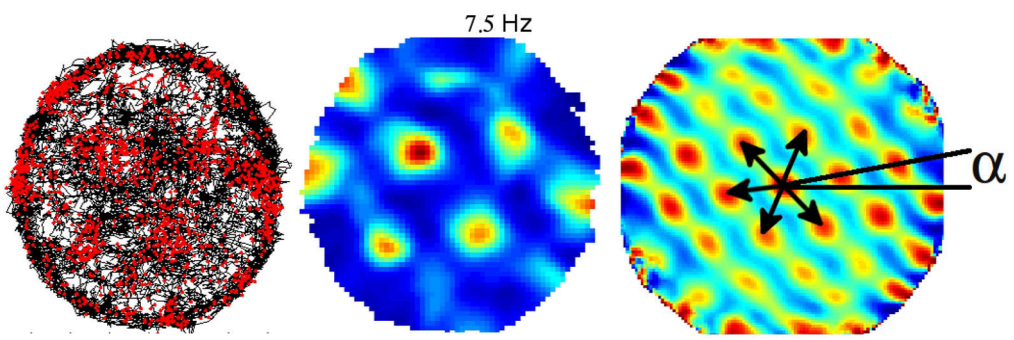


FIGURE 2 | Example of one grid cell recorded from the dorso medial entorhinal cortex (dMEC). Left: trajectory (black) with superposed spike locations (red dots). Middle: color-coded rate map with the peak rate indicated; red is the maximum firing rate, dark blue is zero, pixels not covered are white. Right: autocorrelation matrix of the rate map; the color scale is from blue ($r = -1$) through green ($r = 0$) to red ($r = 1$). Black arrows represent the distances between peaks (the scale of the map), and a represents the angle between the horizontal line and the first firing field array (the orientation of the map). The phase of the map is represented by the position of the firing fields.

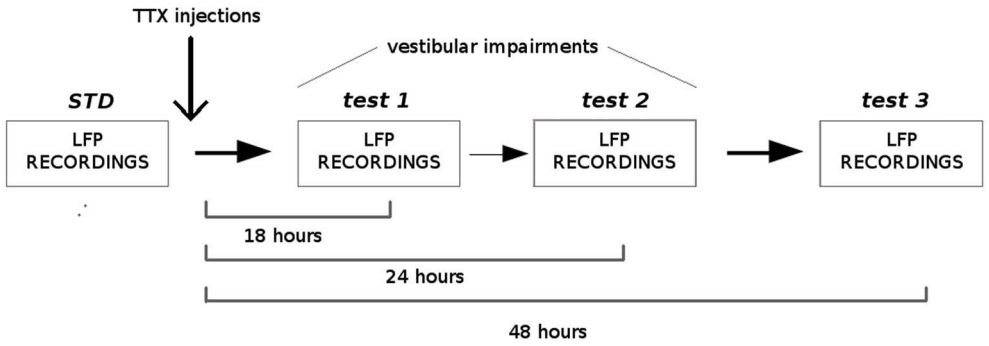


FIGURE 3 | Experimental protocol. Local field potentials (LFPs) from the medial EC were recorded before and, 18 h, 24 h and 48 h after TTX administrations into the middle ear. Before each recording session, vestibular functions were assessed using two different tests: the "contact-righting" test and the "landing" test. All rats displayed vestibular impairments at both 18 h and 24 h delays. Vestibular functions were recovered 48 h after TTX injections.

is no doubt that idiothetic cues do control grid cells' activity and possibly contribute to the generation of their regular firing pattern. Thus, it is likely that the vestibular signal influences grid cell activity, but this issue has not been explored so far. To tackle this issue, we analyzed the effects induced by inactivating the vestibular system on the activity of the medial EC. We provide the first experimental evidence showing that the disruption of the vestibular signal induces a strong disorganization of the activity of the entorhinal neuronal network.

EFFECTS INDUCED BY VESTIBULAR INACTIVATION ON ENTORHINAL CORTEX ACTIVITY

In order to characterize how the vestibular signal influences EC activity, we studied the effects of temporary inactivation of the vestibular system on local field potentials (LFP) recorded within the dMEC. More specifically, we were interested in looking at the possible changes in oscillations in the theta band (5–12 Hz) within the dMEC neural network following disruption of the vestibular signal. According to recent models (Burgess et al., 2007) and experimental data (Brandon et al., 2011; Koenig et al., 2011), these oscillations are necessary to build the grid-like firing pattern. It is therefore likely that if vestibular inactivations disrupt theta oscillations in the dMEC, it would also result in a drastic disorganization of the grid-like firing pattern of the dMEC neurons.

Four adult Long-Evans rats (Janvier, France) were implanted with a bundle of four tetrodes aimed at the dMEC. The following coordinates were used, according to the stereotaxic atlas (Paxinos and Watson, 2004): AP: 0.6–0.8 mm anterior to the sinus, ML 4.8–5.0 mm from midline, DV 1.5 mm under the dura. After one week of recovery, the rats were trained to forage in two different enclosures (150 cm open arena and 150 cm circular track, 15 cm wide) to look for sugar pellets, and the electrodes were progressively lowered to reach the dMEC. When theta rhythm was detected in the LFPs, animals were submitted to the protocol described in **Figure 3**. Each rat was submitted to one-to-four successive recording sessions in each condition (STD (standard), test1, test2, test3), according to their level of exploration and locomotion. During the standard sessions (STD, number of sessions between 3 and 4 per rat, $N = 19$) LFPs were simultaneously recorded between two different tetrodes (one being the reference) at 1.024 Hz and filtered between 0.1 and 500 Hz (Hok et al., 2007). Immediately after the last recording session, the animals received a bilateral

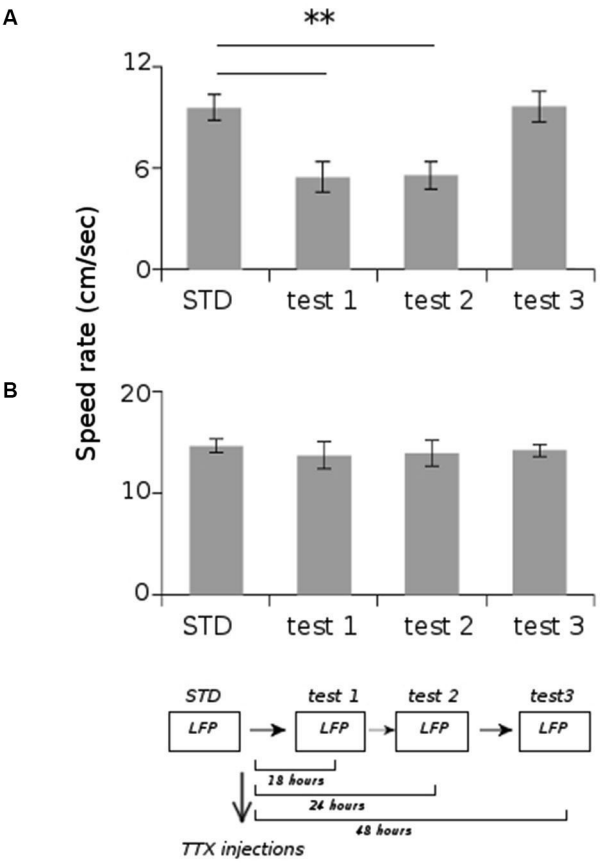


FIGURE 4 | Average locomotion speed rate of the rats during the different recording sessions. **(A)** Total average speed rate. **(B)** Average speed rate excluding the periods of immobility (locomotion speed < 5 cm/s). ** $p < 0.01$, Tukey HSD test.

injection of 0.2 ml of tetrodotoxin (0.6 mM in PBS solution 0.1 M) into the middle ear through the tympanic membrane using a sterile needle (30 G) connected to a 10 ml Hamilton syringe, under general anesthesia (50% medetomidine 0.2 mg/kg and 50% ketamine 75 mg/kg). The rats were left in their home cage to recover from anesthesia. They were then submitted to three blocks of 20 min exploration sessions at 18 h (test 1, number of sessions between 1 and 2 per rat, $N = 9$), 24 h (test 2, number of sessions between 1 and 2 per rat, $N = 9$) and 48 h (test 3, number of sessions between 3 and 4 per rat, $N = 13$) after the TTX injection, and LFPs were recorded as previously described. At each delay, the vestibular dysfunction was assessed using the "landing" posture test and the contact-righting test. In the first test, the rat is lifted gently by the base of the tail. Intact rats extend their forelimbs toward the horizontal surface, whereas vestibular lesioned rats tend to curl their bodies ventrally around and towards their tail (Stackman and Herbert, 2002). In the contact-righting test the rat is placed supine on a tabletop surface and a Plexiglas surface is brought in contact with the ventral surface of the rat's feet. Intact rats will rapidly right themselves whereas rats with vestibular impairments will "walk" about under the Plexiglas surface while in the supine position (Stackman and Taube, 1997). One rat was submitted twice to the entire protocol with a 30 days delay between the two TTX injections. Since no differences in both animal behavior and LFP recordings were observed between the two injections and between exploration of the different enclosures (open arena and circular track), all data were included in the statistical analysis. In order to characterize the oscillations in the theta band before and after TTX administrations, we calculated the Fast Fourier Transform of the power spectral densities and extracted power values in the theta band (5–12 Hz) and the delta band (1–4 Hz) (Matlab, FMA Toolbox distributed under General Public Licence, http://fmatoolbox.sourceforge.net/). We then expressed theta power as the ratio between the power spectrum in the theta and in the delta band. Finally we characterized the correlation between the peak frequency in the theta band and the velocity of the animal by calculating the Pearson correlation coefficient for 1000 ms intervals, for each recording session. The periods in which the rats were immobile or moved very slow (velocity less than 5 cm/s) were excluded from the analysis.

All animals displayed strong vestibular impairments both at 18 h and 24 h, but vestibular function recovered 48 h after TTX injection, as assessed by the landing test and the contact-righting test. In addition, the rats exhibited typical behavioral symptoms of impaired vestibular function at both 18 h and 24 h delays, whereas such deficits were absent at 48 h delay condition. Such changes included head dorsiflexion, flattened posture with limbs adducted and rapid oscillatory head movements in the yaw plane. In addition, vestibular inactivation strongly decreased locomotion speed (**Figure 4A**; ANOVA delay effect $F_{(3,46)} = 78.26$, $P < 0.01$; Tukey Honestly Significant Difference (HSD), STD vs. test 1 $P < 0.01$, STD vs. test 2 $P < 0.01$). However, when all periods of immobility (locomotion speed < 5 cm/s) were excluded, no differences were observed (**Figure 4B**; ANOVA delay effect $F_{(3,46)} = 2.08$, $P > 0.5$). During vestibular inactivation we found a strong decrease of theta power (**Figures 5A, B**, left panel), and no effects on delta power (1–4 Hz normalized to the total power, $F_{(3,46)} = 0.17$, $P > 0.5$). A one-factor ANOVA showed a significant delay effect ($F_{(3,46)} = 0.28$, $P < 0.01$), which reflected the changes in theta/delta power ratio across the different time interval at which LFPs were recorded. Tukey HSD *post-hoc* analysis revealed a significant

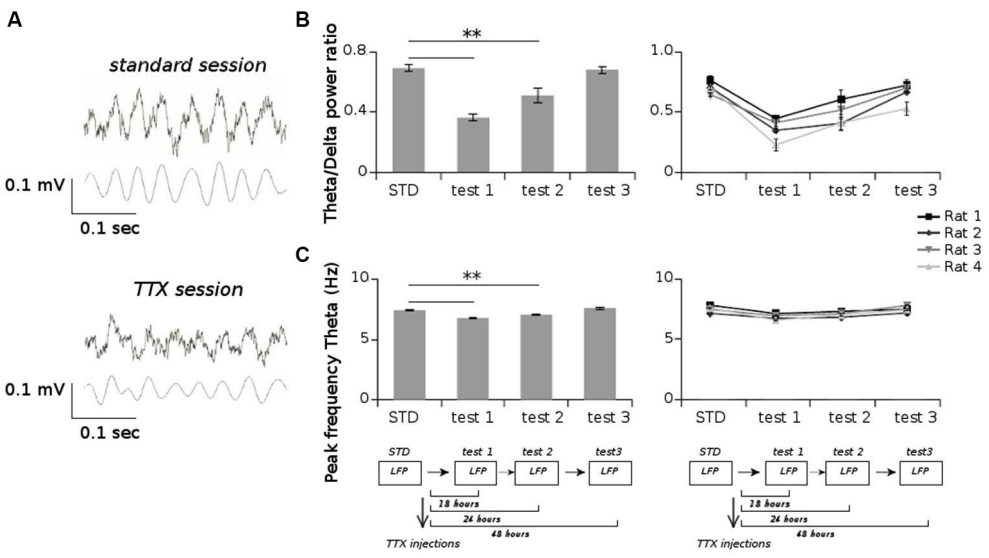


FIGURE 5 | (A) Examples of raw LFPs (upper panels) and filtered LFPs in the theta band (5–12 Hz) (lower panels) from one session recorded before TTX injections (standard session) and one session recorded after TTX injections (TTX session). **(B)** Average values of the ratio of the power spectrum in the theta band (5–12 Hz) and in the delta band (1–4 Hz), for all sessions recorded before and after TTX administrations. **(C)** Average values of the peak frequency in the theta band for all sessions recorded before and after TTX administrations. ** $p < 0.01$, Tukey HSD test.

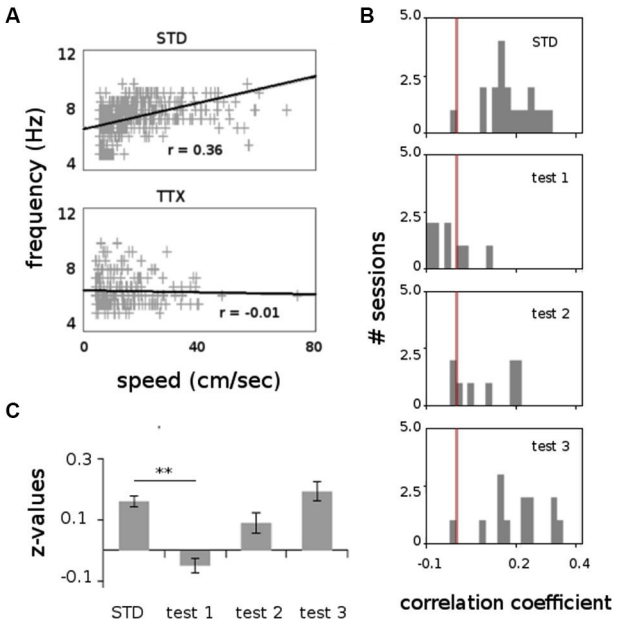


FIGURE 6 | Correlation between speed locomotion and theta frequency (1000 ms bins), before and after TTX injections. (A) Scatterplot showing the relation between speed locomotion and theta frequency in two representative recording sessions before (STD) and during TTX administrations (TTX). Linear regression line and correlation values (Pearson's product-moment correlation) are indicated. **(B)** Frequency distributions for the correlation values for all sessions recorded before and after TTX injections. The red bar represents the value $r = 0$. **(C)** Average values of the correlation coefficient (Fisher z-transformation) between speed locomotion and theta frequency. ** $p < 0.01$, Tukey HSD test.

difference between STD sessions and both test 1 and test 2 ($P < 0.01$), but no difference with test 3 ($P > 0.1$). No significant difference was observed between rats (**Figure 5B**, right panel; Kruskal-Wallis ANOVA H(3, $N = 16$) = 2.50, $P = 0.5$) and a significant difference was observed between the different delay conditions (STD, test1, test2, test3; Kruskal-Wallis ANOVA H(3, $N = 16$) = 11.37, $P = 0.009$). A slight although significant reduction in theta peak frequency was also observed following TTX injection (**Figure 5C**; ANOVA: delay effect $F_{(3,46)} = 1.47$, $P < 0.01$; Tukey HSD, STD vs. test 1 $P < 0.01$, STD vs. test 2 $P < 0.01$). No significant difference was observed between rats (**Figure 5C**, right panel; Kruskal-Wallis ANOVA H(3, $N = 16$) = 3.20, $P = 0.4$) and a significant difference was observed between the different delay conditions (STD, test1, test2, test3; Kruskal-Wallis ANOVA H(3, $N = 16$) = 10.74, $P = 0.013$). Finally we calculated the correlation (Pearson's product-moment correlation) between speed locomotion and theta frequency before and after vestibular inactivations. All periods of immobility were excluded from this analysis. Speed/theta frequency correlation was significant for the large majority of STD sessions ($P < 0.05$ in 16 sessions out of 19). On the contrary, during vestibular inactivations very few sessions showed a significant correlation value (test 1, total sessions $N = 9$, all non significant; test 2, $P < 0.05$ in 4 sessions out of 9). Forty-eight hours after TTX injection, speed-theta frequency correlation tended to be restored (test 3, $P < 0.05$ in 11 sessions out of 13; **Figures 6A** and **6B**). The average values of the correlation coefficients at each delay condition confirmed this effect (**Figure 6C**). The one-factor ANOVA showed a significant delay effect ($F_{(3,46)} = 15.42$, $P < 0.01$). Tukey HSD post-hoc analysis revealed a significant difference between STD sessions and test 1 ($P < 0.01$), but no difference with test 2 and test 3 ($P > 0.1$).

Overall these results demonstrate that inactivations of the vestibular apparatus by trans-tympanic TTX injections provoke a strong decrease in power spectrum in the theta band and totally abolish the coupling between theta oscillations and locomotion speed. This indicates that the vestibular signal exerts a strong influence on the functional properties of the dMEC neural network.

CONCLUSIONS

Path integration involves a large network of brain areas. Among these structures, the EC has been suggested to play a major role (McNaughton et al., 2006; Van Cauter et al., 2013). The discovery of grid cells, together with head-direction cells and conjunctive grid × head-direction cells, in the dorsal medial part of this structure strongly supports this hypothesis (Sargolini et al., 2006). The spatial activity of grid cells shows a relative independence of the environment and is maintained in spite of changes in running speed and running direction in darkness (Hafting et al., 2005). This suggests that vestibular signals mediating velocity and heading must be integrated over time to enable a constant representation of animal position. It is therefore likely that the vestibular system exerts a strong control over grid cell firing patterns. Here we show that vestibular inactivations strongly affect dMEC network activity by (1) decreasing the magnitude of theta oscillations; and (2) abolishing the correlation between velocity and theta frequency. The persistence of somewhat reduced theta

rhythm indicates that such oscillations may be generated by the integration of non-vestibular inputs. However, the absence of theta-frequency speed dependence demonstrates that the vestibular signal is essential for velocity-controlled theta oscillations. Recent studies have shown that inactivations of the medial septum strongly reduce theta oscillations in the EC and abolish the grid-like firing pattern of the dMEC cells (Brandon et al., 2011; Koenig et al., 2011). This effect could be a consequence of the disruption of the velocity signal within the medial septum (King et al., 1998). Both the medial septum and the vestibular system may therefore control grid cell activity through modulation of velocity-controlled theta oscillations in the dMEC.

It is interesting to discuss these results in the frame of the theoretical models of grid field formation. The remarkable regularity of grid patterns has indeed inspired a large number of models over the last eight years. These models are generally divided in two categories, the oscillatory interference models and the attractor models. The first suggests that the firing pattern of the grid cells arises from temporal interference between an incoming theta rhythm and intrinsic membrane oscillations, such as those recorded by Giocomo et al. (2007) (Blair et al., 2007; Burgess et al., 2007; Burgess, 2008). The second postulates that the periodic grids is the result of interactions between local excitatory and inhibitory connections that creates a bump of activity which moves in correspondence with the rat's motion (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Burak and Fiete, 2009; Navratilova et al., 2012). Some models are based on both mechanisms (Hasselmo and Brandon, 2012), others discretize position into direction-dependent stripes or moduli (Gaussier et al., 2007) or small-scale grid networks (Blair et al., 2007) and use spatial interference to create a 2D hexagonal grid. In all cases, however, the velocity signal is essential for modifying and updating the spatial position (but see also Kropff and Treves, 2008). Presumably, such a signal arises primarily from the activity of the VNC. We speculate that inactivations of the vestibular system, which represents the primary input to the VNC, suppress the velocity signal (Angelaki and Dickman, 2000) and as a consequence disrupt the hexagonal pattern of grid cell activity. It should be noted, however, that vestibular impairments may be compensated at the central level by other inputs, such as those provided by the optic flow. Indeed optic flow is able to activate the VNC (Boyle et al., 1985; review in Cullen, 2012) and may provide a speed signal in the absence of vestibular signals. This could explain why in a virtual reality task functional grid cells are recorded and a speed-theta correlation is maintained despite the absence of vestibular motion signals (Domnisoru et al., 2013).

The vestibular system seems to exert a strong control over all categories of place-selective cells but it is unclear whether the mechanism is similar for all cell types. Vestibular lesions or inactivations provoke a drastic disorganization of the activity of place cells and possibly grid cells. In contrast, septal inactivations, which are supposed to disrupt the velocity signal, have a strong impact on grid cells but no effect on the spatial selectivity of place cells (although their firing frequency significantly decrease) (Koenig et al., 2011). In addition, Ravassard et al. (2013) have shown that in a cue-controlled virtual reality task functional place cells exist in the absence of theta frequency-speed dependence. This finding suggests either that the vestibular system influences the activity of place cells in a different manner compared to the grid cells (i.e., independently of its influence on the animal speed), or that different categories of place cells exist based on the sensory input that they receive. It is possible that some place cells are specifically controlled by self-motion cues and therefore influenced by the velocity signal, whereas other place cells are driven mainly by landmarks. This hypothesis could find a support on the observation that in a virtual reality task the percentage of active place cells is significantly lower than that observed in the real world (Ravassard et al., 2013). One may speculate that recording a greater number of place cells should reveal a small population of active place cells following vestibular inactivations.

In conclusion, the vestibular information potentially contributes to grid cell, place cell and head direction cell activity. These neurons form a network that combines self-motion cues and external cues to accurately track an animal's movement through space. Characterizing multisensory integration processes within this neural network helps to understand the cooperation between these cells and the organization of spatial navigation process.

AUTHOR CONTRIBUTIONS

Pierre-Yves Jacob and Francesca Sargolini planned the experiments. Pierre-Yves Jacob performed surgeries and LFP recordings. Martine Liberge and Pierre-Yves Jacob performed vestibular inactivations. Pierre-Yves Jacob and Francesca Sargolini performed data analysis. Pierre-Yves Jacob, Bruno Poucet, Etienne Save and Francesca Sargolini wrote the article. All authors participated to the discussion and the interpretation of the results.

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The development of vestibular system and related functions in mammals: impact of gravity

Marc Jamon*

Faculté de Médecine de la Timone, Institut National de la Santé et de la Recherche Médicale U 1106, Aix-Marseille University, Marseille, France

Edited by:
Stephane Besnard, Institut National de la Santé et de la Recherche Médicale U1075, France

Reviewed by:
Adrian Rodriguez-Contreras, City College of New York, USA
Christian Chabbert, Institut National de la Santé et de la Recherche Médicale, France

****Correspondence:***
Marc Jamon, Faculté de Médecine de la Timone, Institut National de la Santé et de la Recherche Médicale U1106, Aix-Marseille University, 27 Boulevard Jean Moulin, 13385 Marseille Cedex 05, France
e-mail: marc.jamon@univ-amu.fr

This chapter reviews the knowledge about the adaptation to Earth gravity during the development of mammals. The impact of early exposure to altered gravity is evaluated at the level of the functions related to the vestibular system, including postural control, homeostatic regulation, and spatial memory. The hypothesis of critical periods in the adaptation to gravity is discussed. Demonstrating a critical period requires removing the gravity stimulus during delimited time windows, what is impossible to do on Earth surface. The surgical destruction of the vestibular apparatus, and the use of mice strains with defective graviceptors have provided useful information on the consequences of missing gravity perception, and the possible compensatory mechanisms, but transitory suppression of the stimulus can only be operated during spatial flight. The rare studies on rat pups housed on board of space shuttle significantly contributed to this problem, but the use of hypergravity environment, produced by means of chronic centrifugation, is the only available tool when repeated experiments must be carried out on Earth. Even though hypergravity is sometimes considered as a mirror situation to microgravity, the two situations cannot be confused because a gravitational force is still present. The theoretical considerations that validate the paradigm of hypergravity to evaluate critical periods are discussed. The question of adaption of graviceptor is questioned from an evolutionary point of view. It is possible that graviception is hardwired, because life on Earth has evolved under the constant pressure of gravity. The rapid acquisition of motor programming by precocial mammals in minutes after birth is consistent with this hypothesis, but the slow development of motor skills in altricial species and the plasticity of vestibular perception in adults suggest that gravity experience is required for the tuning of graviceptors. The possible reasons for this dichotomy are discussed.

Keywords: vestibular development, critical period, otolith, utricle, microgravity, hypergravity, ontogeny, altricial

INTRODUCTION

Gravity has modeled the evolution of life on Earth, and provides the frame of reference for the body orientation and the integration of accelerations in the various planes of space. Given the importance, ubiquity and stability of the gravitational force during the evolution of life, the organisms have the opportunity to develop without the need to adjust their gravity sensing to the external environment. It seems nevertheless that, in addition to a genetically controlled phase of development for target finding, a stimulus controlled phase is required for the fine tuning of synaptic terminals (Bruce, 2003). Studying the consequences of the development in altered gravity is of prime importance to understand how the system proceeds, and to envisage the consequences for long term space conquest.

The detection of the gravitational force requires specific receptors in charge of detecting linear accelerations. Two otolithic organs of the vestibular system, the utricle and saccule, achieve this function. These gravity receptors utilize a layer of otoconia, consisting of a complex arrangement of mineral and organic substance, that lies over sensory receptor areas. The shearing force produced by the inertial mass of otoconia displaced against the stereocilia of the sensory hair cells allows the detection of linear accelerations, and gravity. In mammals, as in reptiles and birds, the otoconia exhibit the crystallographic structure of calcite (calcium carbonate). On the sensory epithelium, two types of hair cells detect the movement of the otoconia layer: the flask-shaped type I cells, surrounded by an afferent nerve calyx, and the cylindral-shaped type II cells, contacted by afferent buttons. Bipolar vestibular neurons localized in Scarpa's ganglia connect monosynaptically the hair cells and reach the second order vestibular neurons localized in brainstem vestibular nuclei. The vestibular nuclei receive also projections from other sensory modalities including proprioceptive afferences originating mainly from the cerebellum. The otolithic information is thus integrated with the vestibular information from the semi-circular canals, and with other sensory systems such as vision and proprioception. It participates to various functions by means of afferent fibers sent to different organs through vestibular pathways that project to a variety of brain targets.

A basic function of the vestibular system is to maintain the body equilibrium in the gravitational field. This function requires a permanent control of the head and trunk position in space, and

a control of the head in relation to the trunk. Gaze and postural stabilization result from a complex multisensory integration. The vestibulo-ocular tracts are involved in the movement of eyes to maintain the gaze, and the vestibulo-colic tracts innervate the neck muscles to support the head. The vestibulo-spinal tracts innervate the motor neurons of proximal and axial muscles of upper and lower extremities to maintain posture and balance.

The vestibular system has also privileged relationships with the cerebellum through vestibulo-cerebellar and cerebello-vestibular pathways. The gravisensing otolithic organs make direct and indirect connections with several sub regions of the cerebellum, particularly the floculo-nodular lobe, that constitutes the vestibular cerebellum. The cerebellum is a structure critical for the motor control coordination, the timing of movement but is also involved in motor learning and cognition (Fiez, 1996; Ito, 2006).

In addition to the role of the vestibular system in perception, oculo-motor and postural control, there is an increasing evidence for an important role in maintaining and organizing the navigation maps. The internal representation of head and trunk movements processed by the vestibular nuclei influence various cortical areas at the origin of the perception of egomotion. The second order neurons located in the vestibular nuclei project to thalamic nuclei where they converge with visual and somatosensory tracts (Shiroyama et al., 1999). Three main vestibulo-thalamic pathways are involved in the vestibulo-somatosensory and motor functions, in the vestibulo-striatal motor functions, and the vestibulo-visual and visuo-motor functions, respectively. The thalamic neurons process and relay information to various cortical areas (Lopez and Blanke, 2011) including the vestibular somatosensory cortex, the primary and premotor cortex, the cingulate cortex and the hippocampus, where the head direction cells and place cells seem to be strongly tuned to vestibular input. Head direction cell signal is a representation of an animal's perceived directional heading with respect to its environment. This signal appears to originate in the vestibular system (Taube, 2007). Current models suggest that otolithic information is involved in the perception of directional heading (Yoder and Taube, 2009). This function requires also the vestibulo-cerebellar pathway (Rochefort et al., 2013).

They are also accumulated evidence of the involvement of vestibular system in regulating the autonomic system. The stimulation of vestibular fibers modulates the activity of sympathetic fibers. For instance the vestibular system is involved in the regulation of the arterial pressure (Kerman and Yates, 1999) and bone mineralization (Denise et al., 2009). The vestibular nuclei could also regulate autonomous functions through a vestibulo-hypothalamic linkage (Fuller et al., 2002; Murakami et al., 2002).

DEVELOPMENT OF GRAVITY SENSING

The maturation of gravity sensing requires the development of various levels of integration whose basic structures are mainly genetically programmed, but may depend in part on the exposure to the gravitational stimuli (Fritzsch et al., 2001; Fritzsch, 2003). An expanding set of data shows that the development of sensory functions needs the assistance of environmental information, during a critical period of their development, as was shown for hearing (Tees, 1967), vision (Hubel and Wiesel, 1970), and touch (Simons and Land, 1987), and to some extent olfaction (Poo and Isaacson, 2007). As for the other sensory information, the nervous system probably needs environmental experience to calibrate the gravity information during critical periods of the development. This hypothesis was evoked many times (Walton et al., 1992; Ronca and Alberts, 2000; Wubbels et al., 2002) and is one of the key issues in the developmental biology research in space (Moody and Golden, 2000). The existence of a critical period in the development of the vestibular system was reported in fish developed in microgravity (Moorman et al., 2002) or hypergravity (Wiederhold et al., 2003b), as in amphibians (Horn, 2004), and could be a general rule in the development of the vestibular sensitivity. The delimitation of a critical period is complex because the adaptation to gravity involves many structures and functions which mature with a different time schedule, and the complete maturation of the vestibular sensitivity requires a long delay.

The development of vestibular organs follows about the same progression in rats and mice. It starts on the second gestational week and complete maturation is achieved by the 4th postnatal week. The development starts with the formation of the otic placode at E8 (E: embryonic day). At E11 the endolymphatic canal forms, and anterior and posterior semi-circular canals appear at E12. The utriculo-saccular canal and the ampullar crests of semi-circular canals are apparent at E15. The proliferation of hair cells precursors may be set aside as early as E10.5 (Fritzsch et al., 2002; Beisel et al., 2005). Hair cells of the utricular macula begin to divide between E14 and E18 with a gradient from the center to the periphery. They are capable of mechano-transduction from E16 (Geleoc and Holt, 2003). They differentiate in type I and II between E16 and E18 (Kawamata and Igarashi, 1993), and most hair cells are formed at birth. Meanwhile the otoconia form between E14 and E16 (Anniko, 1980) and have fully matured at birth. In parallel with the peripheral organ, the first order vestibular neurons of the vestibulo-cochlear nuclei develop between E11 and E18, and the second order vestibular nuclei differentiate between E12 and E14 (Maklad and Fritzsch, 2003a). The synaptic contacts with sensory epithelium develop between E18 and the end of first postnatal week (Mbiene et al., 1988). The type I cells are only partly surrounded by the calyces until birth. The first calyces with adult type appear at PND4 (PND: postnatal day), and the innervation is comparable to the adult at PND10 (Desmadryl and Sans, 1990).

At birth the vestibular structures are therefore morphologically well developed, but they continue to mature. The number of hair cells increases from PND0 to PND3 then decreases from PND3 to PND7, in relation with a process of apoptosis that started at E19 and reach a peak at PND3 to decrease at PND7 (Zheng and Gao, 1997). The cilia are well differentiated at PND7, and they reach their definitive length at PND32. The utricle and saccule continue to grow until PND32 (Dechesne et al., 1986). The neurons of the vestibulo-cochlear nuclei and the second order vestibular nuclei continue to mature during the two first postnatal weeks (Curthoys, 1979b; Desmadryl, 1991). The vestibular apparatus becomes mature at the end of first postnatal month.

The projections of saccular and posterior cristae are the first afferent fibers to penetrate the cerebellum at E17.5, they reach the uvula and nodulus (Maklad and Fritzsch, 2003b). The cerebellar

anlage has occurred between E9.5 and E11.5 (Chizhikov and Millen, 2003). Purkinje cells are born around E13, at which time they migrate into the cerebellar anlage, and granule cells migrate at the same time (Wang and Zoghbi, 2001). At PND1 the internal granule cell layer becomes recognizable and most granule cells mature between PND4 and PND20, with a peak of synaptogenesis of unipolar brush and granule cells at PND 13. The formation of inner granule cell layer, and granule cells neurogenesis, correlate with an extensive penetration of primary vestibular afferent. Axonal branches of primary vestibular afferent spread into the cerebellar cortex around PND7. Supernumerary climbing cells are eliminated during a critical period lasting between PND15 and PND16 (Kakizawa et al., 2000). This time corresponds to the final maturation of the cerebellum. The state of monoinnervation is achieved at the end of third postnatal week.

The axons originating from the lateral vestibular nuclei reach the cervical cord at E13–E14, the thoracic level one day later, and the lumbar cord before birth. About 40% of the vestibulospinal axons are present in the lumbar cord at birth and the adult pattern is observed at the end of the second postnatal week (Vinay et al., 2000, 2005). The percentage of ankle extensor neurons recruited by ventral horn stimulation in isolated brainstem/spinal cord preparations increases from 3% at birth to 35% at PND3–5 (Brocard et al., 1999). Thus the influence of the pathways involved in innervating antigravity muscles increases during the first postnatal week. The arrival of serotoninergic projections to the lumbar cord is critical for the development of locomotion (Vinay et al., 2000).

At functional level, the first regular afferent discharges appear in the peripheral apparatus at PND4. They increase progressively until PND30 (Curthoys, 1979a; Desmadryl et al., 1986). Vestibular evoked potentials in responses to linear accelerations appear between PND6 and PND8 (Freeman et al., 1999). Nevertheless the immature neural substrate is clearly capable of transducing vestibular input (Krasnov, 1991). First order vestibular neurons respond to low frequency acceleration from birth. Not only the major milestones of vestibular morphological vestibular development occurs prenatally, the system is functioning before birth as well (Ronca et al., 2008).

EFFECTS OF ALTERED GRAVITY ON THE DEVELOPMENT OF GRAVITY SENSING

It is impossible to remove gravity on Earth, thus experiments of deprivation of gravitational stimulus during rat development were limited to the exposure to microgravity during space flight. The missions embarked either pregnant females (Cosmos 1514: E12–E17; STS 66: E8–E19; STS70: E10–E19) or nursing litters (STS-72: PND14–PND30; STS-90: PND8–PND24), but longer exposures were not available due to the technical limitations of shuttle flight. Information was more easily obtained from ground experiments using centrifuges to produce hypergravity. Nevertheless the interpretation of these experiments is limited by the different periods of exposure, the intensity of gravity, the type of centrifuge itself, the age of testing and the species used. The alteration of gravity environment during the development involved changes at various levels of integration of the signal, often with opposite effects between hypergravity and microgravity conditions.

OTOCONIA

Several studies showed that the size of otoconia is regulated to achieve a desired weight in a graded manner when the animals are subjected to altered gravity during the development of their statholits. Consequently the size of otoconia is increased in microgravity, and decreased in hypergravity. This process was observed in different species including snails (Wiederhold et al., 2003a), aplysia (Pedrozo et al., 1996), fish (Wiederhold et al., 1997; Anken et al., 2001, 2002a,b; Wiederhold et al., 2003a,b), Xenopus (Lychakov and Lavrova, 1985), chicken (Hara et al., 1995), hamsters (Sondag et al., 1996), rats (Lim et al., 1974; Krasnov, 1991). At variance the otoconia of animals exposed to altered gravity at maturity did not show any change (Lim et al., 1974; Ross et al., 1985; Hara et al., 1995; Sondag et al., 1995). Some of these results supported the existence of a critical period during the development of otoliths (Wiederhold et al., 2003a,b).

SENSORY EPITHELIUM

The exposure to altered gravity also affects the sensory epithelium with variable consequences depending on the period of development. Rats centrifuged (1.75 and 2G) from E9 and sacrificed at E19 showed an increased innervation of vestibulo-cerebellar fibers in the utricle (Bruce et al., 2006). This result, in a period that corresponds to the connection of vestibular afferents to the calyces, suggested that the increased stimulation of hair cells increased the rate of maturation of the utricle. At variance a decreased field of innervation was observed in rats exposed to microgravity during the same period (Bruce and Fritzsch, 1997; Bruce, 2003; Bruce et al., 2006). On the other hand, rats centrifuged (2G) from E9 until 1 week after birth did not show any modification in the time course of the establishment of fibers and calyces (Gaboyard et al., 2003). Thus the peripheral neuritogenesis was not modified by hypergravity 1 week after birth. At variance the utricles showed a delayed terminal location of the microvesicles at the apex of calyces that corresponded rather to a delay in the maturation of type I hair cells. Hypergravity was estimated to delay the synaptic stabilization of hair cells by 4 days (Brugeaud et al., 2006). At variance, rats exposed to microgravity postnatally (from PND8 to PND25) did not show any defect in the pattern of development (Dememes et al., 2001). These results support the hypothesis of a critical period for vestibular plasticity to occur between birth and PND8.

Overall these results suggest that the overstimulation of hair cells during the prenatal period of the formation of the epithelia contributes to accelerate the development of the sensory connections, but after birth the system corrects the tuning to adapt to the over stimulation with durable modifications of the vestibular epithelia.

VESTIBULAR NUCLEI

Exposure to altered gravity during the vestibular development has also consequences on the vestibular nuclei. In fish, the exposure to microgravity increased the number of synapses in some vestibular nuclei (Anken et al., 2002c). In newborn rats the exposure to

microgravity induced a delay in the maturation. Rats exposed to microgravity from half their gestational period showed a delayed synaptogenesis of vestibular nuclei (Savel'ev et al., 1998; Yates et al., 2003) and altered morphology of the cortex, cerebellum and vestibular system (Keefe et al., 1986) that were interpreted as signs of retarded cell development and migration (Alberts et al., 1985). Delayed neuronal development and cell migration was observed immediately after flight (Malacinski et al., 1989), but no change persisted in 15 days old rats. Rats flown prenatally from E8 to E19 showed decreased projections from the saccule to the medial vestibular nucleus, with a reduced branching of the axons, while other vestibular afferents, probably those transducing angular accelerations may have compensated synaptogenesis by increasing synapses number in vestibular nuclei (Ronca et al., 2008). The preponderance of canalar synapses was interpreted as the result of the over stimulation of angular accelerometers due to the abundant rolling movement of the dam during the space flight (Ronca et al., 2008). Even rats exposed to microgravity only during their postnatal development (from PND8 to PND24) showed markedly smaller vestibular cell bodies and less growth of dendritic cell branching with a lack of development, paucity of cerebellar projections to vestibular nuclei (Raymond et al., 2003), and a reduction in motor dendritic tree size and complexity (Walton et al., 2003). These results suggested that the period of sensitivity persisted during the second and third postnatal week in vestibular nuclei, at variance with the sensory epithelium. Contrary to the microgravity, rats centrifuged (1.5G) from E9 to E19 showed a complex segregation of terminal fields of saccular axons into the four laminae (Bruce and Fritzsch, 1997; Bruce, 2003). This result was opposed to the poorly developed saccular axons in the medial vestibular nuclei of rats exposed to microgravity during the same period. The faster rate of vestibular maturation of rats exposed to hypergravity was confirmed by the faster maturation of peripheral utricular connections in rats centrifuged (1.5 and 2G) from E10 to E20 (Bruce et al., 2006). These results suggested that the exposure of microgravity retarded the development while the exposure to hypergravity advanced the maturation.

CEREBELLUM

Effects of microgravity exposure on the vestibular nuclei of rats flown between PND8 and PND24 showed that space flight profoundly affects the postnatal development of cerebellar branching in the vestibular nuclei of rats (Raymond et al., 2003). The effects of hypergravity on the vestibulo-cerebellar connections were analyzed in details by Sadjel-Skulkowska and collaborators. Their experiments on rats exposed to hypergravity (1.5 and 1.75G) during the almost complete development of vestibular system (from E8 to PND20) showed a decreased mass of the forebrain and particularly of the cerebellum at PND6-PND9 then at PND21 (Sajdel-Sulkowska et al., 2001; Ladd et al., 2006), in relation with a decreased number of Purkinje cells (Sajdel-Sulkowska et al., 2005) that could be related to a transient hypothyroidism induced by hypergravity (Sajdel-Sulkowska et al., 2001, 2005). Other analyses carried out during limited parts of the development showed two periods more sensitive to hypergravity: the second gestational week that coincides with the period of Purkinje cells birth, and the 2nd and 3rd postnatal weeks that coincide with the peak in granule cell neurogenesis (Nguon et al., 2006b). The alteration of cerebellar development in centrifuged rats could be related to a change in the quantitative or temporal expression of proteins involved in cell-cell interaction (Sajdel-Sulkowska, 2008).

DESCENDING PATHWAYS

At the level of the spinal cord, hypergravity induced a delay in the development of descending pathways, including reticulo- and vestibulo-spinal tracts, (Brocard et al., 2003) and a hyperactivity of lumbar motoneurons (Krasnov et al., 1992). The development in hypergravity also provoked a substantial delay of the development and strong perturbations of monoaminergic projections to the spinal cord in newborn rats centrifuged (1.8G) from E10 to PND15. An anarchic pattern of innervation, with numerous dystrophic profiles mainly of serotonergic system, was present at PND 15 and persisted in 8 months old animals, suggesting that rats submitted to hypergravity during the critical period of onset of monoaminergic projections to the spinal cord are affected durably in the organization and the ultrastructure of these projections (Gimenez y Ribotta et al., 1998). Neonate rats flown postnatally in a spaceflight from PND8 to PND24 showed a reduced development of dendritic trees in a population of motor neurons innervating axial and proximal muscles (Inglis et al., 2000). This observation suggested a possible reduction of the synaptic activation of these motor neurons due to the hypo activation of the otolithic system in microgravity.

These studies suggested that altering gravity perturb the connectivity of vestibulo-spinal pathways. Together these results suggest that the motor development was delayed when the gravity sensing system was either overstimulated or deprived. They demonstrate that the environment plays a critical role in fine-tuning of axons, and for appropriate development of the projections from gravity receptors to the brain and spinal cord.

COGNITION

The possible consequences of the early exposure to altered gravity on the cognitive development is a pending question because cognitive alterations have been reported in adults exposed to altered gravity. There are two main ways of action of gravity on the cognitive functions. On the one hand, the organization of somatotopic maps is strongly influenced by sensory experience early in life and to a lesser extent in adulthood. The somato-topic maps in primary somatosensory cortex constitute neural networks which play a pivotal role in sensory integration and perceptual learning. Long-lasting changes in the properties of somatosensory cortical neurons and discrimination abilities have been reported after early alteration in tactile experience (Coq and Xerri, 2001). Hypergravity or microgravity change the representations of muscles in the somatosensory cortex of adult rats (D'amelio et al., 1998a,b; Trinel et al., 2013). The durable consequences of early motor experience in altered gravity on the somatosensory maps are unknown, but a study on rats flown in the space station for 16 days from PND14 to PND30 showed durable changes even after 4 months (Defelipe et al., 2002). On the other hand, there is a convergent opinion that changes in peripheral and central vestibular neurotransmission contribute to the impaired spatial

learning through decreased vestibular inputs to areas important for spatial cognition such as the hippocampus. The hypothesis of a role of vestibular inputs on spatial cognition is supported by the demonstrations that loss of vestibular function alters spatial cognition (Brandt et al., 2005; Ventre-Dominey et al., 2005; Smith et al., 2010). A possible explanation for the role of vestibular input on the impairment of spatial learning could be related to a mismatch of the otolithic contribution to the head direction cells (Stackman and Taube, 1997; Taube, 2007; Yoder and Taube, 2009). The influence of gravity on the spatial impairment is supported by changes in the expression of hippocampal genes specifically modulated by hypergravity (Del Signore et al., 2004) or microgravity (Santucci et al., 2012), but changes in the gene expression in the hippocampus was observed also in tail suspended mice, a situation that do not alter gravity sensing (Sarkar et al., 2006). The specific contribution of the altered gravity in the gene expression of the hippocampus is therefore always questionable. Alternately altered cognition and the change of genes expression in the hippocampus could reflect changes in the brain-hypothalamic-pituitary-adrenal axis due to the chronic stressful experience, involving a stressor specifically associated to hypergravity (Del Signore et al., 2004). This hypothesis is supported by the existence of a hypothalamic-pituitary-adrenal axis activation induced by vestibular lesions (Gliddon et al., 2003a,b). Gravity changes could also alter cognitive function via modulation of brain vascular reactivity (Porte and Morel, 2011). In addition, high levels of hypergravity induce severe impairments in cognitive abilities which may be associated with brain ischemia (Sun et al., 2009). An influence of hypergravity on the performance of adult rats and mice in spatial memory tests was observed after chronic centrifugation (2G) for 2 weeks (Mitani et al., 2004) or after repeated episodes of 1 h of centrifugation (1.85G) during 5 days (Mandillo et al., 2003), or after short exposure (3 min) to high level of hypergravity (6G) (Cao et al., 2007; Sun et al., 2009). The information about the effect of altered gravity during the development of the cognitive functions was rarely studied. Except for the exposure of peri-adolescent mice to short episodes of acute centrifugation (Francia et al., 2004; Santucci et al., 2009), the unique analysis of cognitive function in rats flown postnatally between PND 14 and 31 did not show any difference in spatial orientation or brain structure (Temple et al., 2002).

VESTIBULAR REACTIONS

The evaluation of vestibular efficiency in neonate rodents is mainly based on the observation of righting reflex. The righting from a supine to a prone position is a basic motor pattern that rat and mice pups are able to perform on the first postnatal day (Roubertoux et al., 1985; Pellis et al., 1991), because it is necessary to reach the nipple (Eilam and Smotherman, 1998). Testing the righting reflex is done by means of contact righting, or water immersion, or air righting, to avoid proprioceptive information to aid the response. The righting response involves the proper dynamic interaction of otolith dependent vestibulo-colic and vestibulo-spinal reflexes, and otoconia deficient mice are unable to perform righting response.

MICROGRAVITY

A few space missions allowed either a prenatal or a postnatal exposure to microgravity. Rats flown in a space flight prenatally (E8–E19) showed an early righting impairment that was recovered from PND5 (Ronca and Alberts, 1997, 2000; Ronca et al., 2000, 2008). Eventually, they did not show any change on successive timing of hind limb motor development over a period of 81 days after landing (Wong and Desantis, 1997). Rats exposed postnatally to the space environment (from PND15 to PND24 or from PND14 to PND 30) were able to swim (Temple et al., 2002; Walton et al., 2005a), and to perform surface righting at landing time. This result is contradictory with the inability to float of otoconia-deficient mice and suggest that the vestibular apparatus and vestibulo-colic reflexes were functional within hours of landing. The vestibular information required for this reflex was therefore not altered by microgravity. Nevertheless postnatally flown rats showed impaired maturation in the acquisition of adult tactics of surface righting, and the pups flown until PND30 were definitely unable to perform adult tactics for surface righting (Walton et al., 2005b). For the authors the impairment was probably not due to a sensory deficit, but rather to the missing acquisition of the correct motor pattern during a critical period of motor development. Other long term modifications of motor parameters were observed after the postnatal exposure to microgravity (Walton et al., 1992, 2003, 2005a; Walton, 1998), but they are supposed to be related to strong consequence of gravity on the muscles properties and muscle representation in the brain (Defelipe et al., 2002). They are not considered here as direct consequences of an alteration of gravity sensing. The exposure to microgravity seemed to cause a delay in the acquisition of vestibular reactions during prenatal development, whereas the consequences on postnatal development concerned the acquisition of motor skills. Even though they provided relevant results, the conclusions of these experiments are minored by interrogations concerning the good fit of the flight opportunity with potential critical periods. Ronca et al. (2008) suggested that exposure to microgravity throughout the entirety of neurovestibular development likely produce irreversible or at least enduring deficit in vestibular response. Unfortunately the technical limitations of spaceflight missions do not allow to expose rodents for large part of their development.

HYPERGRAVITY

Several experiments exposed mammals to hypergravity during the complete maturation of the vestibular system. A first experiment centrifuged hamsters from conception to at least 4 weeks and showed reduced performance in swimming ability and air righting that prolonged after months, particularly in hamsters centrifuged until 20th postnatal week. These results were interpreted to reflect a dysfunction in the otolithic system (Sondag et al., 1997). Later studies on rats did not confirm this result. A similar experiment performed on rats did not show differences between hypergravity and control rats (Wubbels and De Jong, 2000), but experimental artifacts possibly interfered. In another study, rats centrifuged (1.75G) from E8 to PND21 showed a poor score on the rotarod at PND21 (Nguon et al., 2006a). The authors correlated this bad performance with a decreased cerebellar mass. Other experiments on rats centrifuged (1.8G) from

conception to PND21 or PND27 showed a delay in the vestibular reflexes that persisted at PND40 (Bouet et al., 2004b). Another study on rats centrifuged until the age of 3 months showed that a complete behavioral recovery occurred in a delay of 3 weeks (Bouet et al., 2003, 2004a). Mice centrifuged (2G) from conception to PND30 showed a delay in the acquisition of maculo-ocular reflex (Beraneck et al., 2012). At the age of 2 months they were not impaired in vestibular response, but showed a tendency to react slower during free fall that was supposed to result from a perturbation of the connections between vestibular, cerebellar and motor structures (Bojados and Jamon, 2012). Together the hypergravity studies suggested that centrifuging during the full development induced transitory vestibular impairment and a possible alteration of vestibulo-cerebellar connections, but the effects were not as drastic in rat and mice than in hamsters. That discrepancy lets open two possibilities: (1) the persistent impairment in hamsters was related to a different development in cricetidae, although the time schedule of development is rather similar to the rats. (2) detrimental effects of the exposure to hypergravity on the vestibular system could be caused by excitoxicity in relation with the duration of exposure (Beraneck et al., 2012).

PRENATAL CENTRIFUGATION

Rats centrifuged (1.8G) from conception to PND10 showed a slight delay in the acquisition of vestibular reflexes that was restored within 21 days (Bouet et al., 2004b). Mice centrifuged during the same period and tested at the age of 2 months were not perturbed in the vestibular tests, and even tended to improve their performance. In addition they showed specific improvement of their aerobic capacities, and a change in postural parameters (Bojados and Jamon, 2012; Bojados et al., 2013). These results showed that vestibular performance was not definitely affected by a prenatal exposure to hypergravity, whereas other changes were definitive. When centrifugation of rats was limited to the second or third gestational week, only the former period induced an impaired equilibrium performance on the rotarod at PND21. This result suggested a possible critical period during the second gestational week in relation with the birth of Purkinje cells at E13–E14 (Nguon et al., 2006b).

POSTNATAL CENTRIFUGATION

Postnatal exposure to hypergravity was rarely studied, but rats centrifuged during the second and third weeks of postnatal development showed the more critical sensitivity to hypergravity exposure (Nguon et al., 2006b), as showed the worst performance on the rotarod at PND21. This postnatal period corresponds to a peak in granule neurogenesis, a period that appears to be critical with respect to the maturation of cerebellar structure and function. Mice centrifuged (2G) from PND10 to PND30 were not significantly impaired in the maculo-ocular reflex (Beraneck et al., 2012), but they showed slower vestibular reactions during the drop tests, in addition to changes in the motor pattern (Bojados et al., 2013). The experiments on postnatal exposure to hypergravity suggest that long term impairment was probably related to the connection between vestibular and cerebellar and motor structure.

STUDIES ON VESTIBULAR DEFICIENT MUTANT MICE

Alternative strategies using ground-based experiments take advantage of the development of targeted mutations in mice. More than 25 lines of mice with congenital vestibular mutations were available in 2002 (Anagnostopoulos, 2002), and the number is increasing. Vestibular deficient mice with a null mutation of the KCNE1 potassium-channel gene that leads to the degeneration of hair cells (Vetter et al., 1996) show a permanent shaker/waltzer phenotype (Vidal et al., 2004) that is caused by dopamine asymmetry due to the absence of vestibular input in the striatum during critical period of the development. The complete removal of vestibular organs before PND5 leads to permanent head bobbing in adults (Geisler et al., 1996; Geisler and Gramsbergen, 1998). This phenomenon was related to the lack of semi-circular canals input rather than the lack otolithic afference (Eugene et al., 2009). Other mutations affect more specifically the graviceptors. Several lines of mice have specific alteration of genes involved in the formation of the otoconia while other components of the vestibular system are intact (Ornitz et al., 1998). The shaker/waltzer phenotype is not observed in these otoconia-deficient mice. They have a typically permanent head tilt phenotype that could be the signature of an otoconial critical period. Studies of mouse strains with graded otoconial deficiencies showed graded loss of function, and confirmed the absence of linear acceleration vestibular evoked potentials in mice lacking completely otoconia (Jones et al., 2004). Morphometric analyses of the vestibular ganglia performed at various stages of the postnatal development of *tilted* mice showed a slower development during the first postnatal week (either rate of development or cell number), then they reached values similar to control, and eventually possess normal appearing sensory epithelia. The absence of gross abnormality in the vestibular ganglia may be due to the spontaneous activity of receptor cells which maintain tonic stimulation of the ganglionic cells (Smith et al., 2003). It was demonstrated that the presence of otoconia is not required for the general formation and maintenance of synapses (Hoffman et al., 2006) or normal development of vestibular ganglia (Smith et al., 2003). Mutant mice, with the tilted mutation (*tlt*) that eliminates an essential component necessary for the formation of otoconia, can learn gravity dependent motor task by using semi-circular canals and limb proprioception to compensate otoconia deficiency (Crapon De Caprona et al., 2004). However head tilt (*het*) mice with a recessive mutation causing a complete lack of otoconia are unable to perform task requiring equilibrium or postnatal reflexes and do not perform righting response. They show also an alteration of working spatial memory and place recognition (Machado et al., 2012), that is supposed to be originating from an abnormal modulation of head direction cells.

There are major limitations with the use of mutant lines to evaluate the consequences of specific alterations of the vestibular apparatus, because most mutants may have potentially compromised hair cells, stereocilia or vestibular ganglia, due to the expression of mutated genes in these structures. In addition the definitive removal of graviception is susceptible to produce compensation mechanisms (Crapon De Caprona et al., 2004). For instance, in the *IED* (Inner Ear Defect) mice, in the absence of otolithic information, visual inputs become instrumental for

gaze stabilization (Beraneck et al., 2012). Nevertheless the generation of inducible conditional knockout mice, which allows selected inactivation of genes in tissues at a given time point, is of prime importance to complement micro- and hypergravity studies.

THE HYPOTHESIS OF CRITICAL PERIODS IN THE ADAPTATION TO GRAVITY

A survey of the literature covering the last decade shows that many of the consequences of the exposure to altered gravity during the development of vestibular sensitivity were supposed to involve a critical period. The existence of critical period was invoked about the development of gravity sensing concerning the peripheral organ (otoconia, sensory epithelium), the vestibular nuclei, the cortical projections, the cerebellar connections, and the motor output. In most cases the critical periods were hypothesized when a definitive or at least a long lasting change was observed after the exposure to altered gravity during some developmental stages. The long term duration of the change is not mandatory and some authors prefer to use the term of sensitive period. In addition, further events occurring during the life history are susceptible to reduce or to mask the changes induced during a critical period (Bojados and Jamon, 2012). A more precise assessment of the meaning of critical period have an heuristic value for understanding the consequences of the exposure to altered gravity on developing structures.

A critical period is a time window of the early life when the experience of external information is needed for the normal development of a structure or a function. The brain needs this external sensitivity period to tune the receptor with the source when precise information about the individual or the environment cannot be predicted and therefore cannot be genetically encoded. The critical period corresponds therefore to an interactive specialization in the functional organization of brain regions or cortical areas. A critical period can only open when the structure concerned has achieved its embryological development. GABAergic neurons have a main role in the internal control of critical period timing. For instance the onset and duration of visual critical period is advanced in mice over expressing BDNF, that accelerate maturation of GABAergic neurons (Huang et al., 1999). At variance the critical period for ocular dominance is inhibited in mice lacking Gad65 gene, that show poor GABA release, and is restored with diazepam which acts as a GABA agonist (Hensch et al., 1998).

In addition to the internal process, relevant sensory information is required, and the critical period can be delayed and prolonged to some extent when the information is not available. Dark rearing, for instance, delays the maturation of GABAergic transmission and the onset of visual critical period, but BDNF supplementation abolishes this delay (Hensch and Fagiolini, 2005). The termination of the critical period is a consequence of the mechanisms by which the cortical regions become increasingly specialized and fine-tuned. Changes in the brain neurochemistry as for instance the composition of N-Methyl-D-Aspartate (NMDA) receptor increase the rate of pruning of synapses and results in a freezing of the pattern of functional sensitivity.

The achievement of the critical periods involves three main stages (Hensch, 2004): (1) expansion of axonal branching and synapses formation in association with a high level of grow associated proteins and neurotrophic factors, particularly BDNF. With this process neurones invade narrow brain regions and elaborate new projection fields, the response properties of cortical regions interact and compete to acquire their role in new abilities; (2) a further shaping of the circuit architectures is realized by pruning less solicited axons and synapses, on the basis of the competition between neural inputs on common targets. The structural consequences of the functional competition for brain regions was illustrated by the lateral dominance occurring in the cortical mapping of sensory entries after hemi deprivation of vision, audition or somatosensory system; (3) structural stabilization of potentiated synapses by the insertion of cell adhesion molecules, change in the composition of NMDA receptor and limitation of GABAergic large basket cells in an extracellular matrix. The consolidated synapses become invulnerable to further elimination and make further plasticity harder to occur.

On the basis of the theoretical process of critical period, two main consequences are expected from the lack of gravity sensing during the development in microgravity: (1) a delayed maturation is expected because the onset of critical period is prevented by the unavailability of the sensory information. This should leave immature characteristics in the system; (2) A colonisation of gravity related vestibular projections by competing afferences, particularly the expansion of inputs from the angular acceleration detectors which continue to be stimulated in microgravity. These expected consequences are consistent with the delayed maturation reported in rats flown prenatally. For instance, rats exposed to microgravity during the second half of the gestational development showed a delay in the synaptogenesis of saccular neurones and an increased proportion of angular acceleration synapses (Ronca et al., 2008). These observations were supposed to involve an overstimulation of canalar inputs *in utero* due to the 3D movements of the floating dam (Ronca et al., 2008), but they are also consistent with delayed development and competition for neural branching, and therefore support the existence of a critical period. In the same way the possibility was evoked for otolithic deficient *IED* mice that in the absence of gravity related signals central vestibular neurons would substitute otolith inputs with spatially non matching canal inputs (Beraneck et al., 2012).

Hypergravity can be considered as a mirror situation to microgravity (Serova et al., 1985; Serova, 1991; Phillips, 2002; Wade, 2005). From the point of view of critical period, the situation is not symmetrical however. Obviously sensory deprivation does not apply to this situation. In the hypergravity environment, the gravitational stimulus is not removed, but increased instead, producing therefore an overstimulation with reference to the other stimuli. It is important to distinguish between overstimulation, under stimulation and deprivation. Nevertheless two logical consequences of the concept of critical period apply to hypergravity: (1) A possible faster maturation instead of a delay in maturation due to the hyper stimulation; (2) The expansion of gravity related pathways at the detriment of competing afferences. From this point of view, it is noteworthy that various effects observed in rats developed in hypergravity were

associated with faster rates of embryo maturation (Bruce et al., 2006). Indeed several pieces of information seem to comfort the advanced maturation of the peripheral organ when exposed to hypergravity during the morphological development of structures. On the other hand other studies concluded to a retarded development and the persistence of impairments. The interaction of multiple structures, each with different time schedule, produces a complex situation when the developing organisms are exposed to hypergravity, and induces potential factors of trouble at the origin of this dichotomy. Four of them are listed below:

1. The advanced maturation of the vestibular apparatus, that can be theoretically expected in case of overstimulation during a critical period, is susceptible to perturb the synchrony with later developing structures, as for instance the cell-cell interaction between vestibular and cerebellar structures. Note that reciprocal consequence apply to the delayed development of vestibular structures in microgravity. This could explain why both micro- and hypergravity induce a perturbation in vestibular-related structures.
2. The sensory system adapts to the over intensity of the gravity signal by reducing the otoconia mass, the connections in the maculae, and the hair cells responses. Consequently, the vestibular apparatus is under tuned for Earth gravity. This could be another source of dysfunction during the establishment of connections with other structures, and then could participate to the impairment of the vestibulo-cerebellar or vestibulo-motor functions.
3. Due to the competition of sensory entries for neural targets during the critical periods, the overstimulated otolith structures should be overrepresented in vestibular nuclei and brain targets, at the detriment of the canalar afferences. This disequilibrium is a potential source of trouble because the otolithic and canalar afferences are heavily mixed to contribute to the vestibular signal.
4. The prolonged exposure to hypergravity could have detrimental effects on the vestibular system by excitotoxicity due to the overstimulation, as occurs for other sensory entries (Peusner, 2001). This effect should be dependent on the duration and probably of the intensity of the overstimulation, and could explain some long term deficiency observed after a long period of centrifugation.

THE VESTIBULAR DEVELOPMENT IN PRECOCIAL OR ALTRICIAL SPECIES

The analysis of vestibular development refers either to prenatal or postnatal exposure to altered gravity. The consecutive differences are basically related to the development of the vestibular apparatus, that is mainly prenatal, and vestibular-related functions that develop heavily after birth. The vestibular and motor immaturity contribute to the unachieved postural and motor control observed in rats and mice (Clarac et al., 1998; Muir, 2000), even though behavioral adaptations contribute to the silencing of motor activities in nesting mammals (Jamon, 2006). The immaturity of postural control at birth opens speculations about a possible role of the experience *ex utero* for the maturation of postural control. At variance, precocious species are relatively mature and mobile at birth and acquire rapidly the adult-like motor control. Typically altricial species have poorly developed offspring, with eyes and ears closed at birth, virtually no hairs on the body, and are typically born in multiple litters, whereas precocial species have well developed offspring with eyes and ears open at (or soon after) birth, hair coat well developed, and are typically born as singletons. Altricial and precocial mammals exhibit no difference in the rate of growth (Case, 1978), and show similar trend course of neural development (Clancy et al., 2001), with the only difference being the arbitrary point of birth (Brunjes, 1988). The longer gestation period in precocial species results in increased development of the central nervous system at birth (Sacher and Staffeldt, 1974). The duration of gestation is therefore the main factor of maturity at birth. The comparative development of guinea pig and rat shows a typical example of the difference in the level of maturity at birth. In guinea pig the gestation lasts 66 days on the average. General movements emerge between E24 and E34 in guinea pig fetuses. The period of E35–E40 is characterized by an established link between the vestibular apparatus and vestibular ganglia (Heywood et al., 1976; Sobin and Anniko, 1983), and myelination of vestibular nerve begins about E40. Cortical differentiation occurs between E41 and E45 (Van Kan et al., 2009). The righting reflex develop *in utero* between E50 and E66 (Sekulic et al., 2009). Standing and walking at present from E63 (Avery, 1928). The motor abilities of precocial species suggest that vestibular functions have matured *in utero*. Even though intrauterine cavity is similar to a microgravity environment (Wood, 1970; Sekulic et al., 2005; Meigal, 2013) because of neutral buoyancy in the amniotic fluid, the otoliths in the intrauterine environment are constantly exposed to the effects of gravity, and are stimulated by the linear accelerations induced by the movements of the mother (Ronca et al., 1993). In addition hair cells do not need the gravitational stimulus to develop. Therefore postnatal experience is no necessary for the system to mature. The process of postnatal maturation in altricial species is therefore independent of vestibular-driven afference. Nevertheless the system continues to develop in precocial species, as well as in altricial species in relation with increasing hair cells number (Jones and Jones, 2000) and the vestibulo-ocular reflex in relation with the increasing size of canals (Straka, 2010). This supports the possibility that the vestibular system is finely tuned with the development of posturo-motor functions. Developing young mice are subjected to direct and indirect effects when exposed to altered gravitational field (Alberts and Ronca, 2005). Among them, the high level of interaction between the mother and pups, particularly in altricial species, is susceptible to be perturbed. The mother and pups constitute a "maternal-offspring system" of paramount importance for the proper development of the young (Ronca, 2003; Alberts and Ronca, 2005) by directing and regulating postnatal development. Licking and grooming are important sources of stimulation that contribute to the brain development. These maternal cares stimulate the expression of BDNF and other neural systems (Curley et al., 2011) in brain parts, resulting in improved emotionality, sociality and learning abilities of pups (Caldji et al., 1998; Liu et al., 2000; Branchi

et al., 2013), and their perturbation is detrimental for cognitive development. Given the importance of BDNF, GABA and glutamate in the regulation of critical periods, the consequences of altered gravity on the maternal care deserve to be investigated further. This aspect could be investigated by means of comparative developmental studies involving altricial (rat and mice) and precocial (Acomys, mesocricetus) species subjected to altered gravity.

CONCLUSIONS

The present review showed accumulating evidence on the sensitivity of the organisms to the alteration of gravity during their development. The peripheral sensory organ adapts to the level of gravity by adjusting the mass of otoconia and the innervation of sensory epithelium. The over or under stimulation advances or delays the maturation of neural connections during the formation of the vestibular apparatus, resulting in inadequate temporal synchrony or sensibility tuning during the connections with vestibular-related structures, and with potential long-term change in the resulting functions. These results provide further evidence that the gravistatic sensory system has a genetically controlled phase of development for target finding and a stimulus-controlled phase for fine-tuning synaptic terminals. Therefore the level of gravity plays a critical role in fine-tuning of axons and is required for appropriate development of the projections from graviceptors to the brain and spinal cord. Several critical periods for the adaptation to gravity are probably spread along the developmental process, in relation with the timing of the various structures involved, and with variable incidence depending on the plasticity of the structures. The time windows of possible critical periods in the development of the various structures can be hardly answered due to the difficulty to remove gravity vector from Earth environment and the limited access to space missions for rodent studies. This question could be answered with long duration space flight as promised the ISS, but does not seem realistic at present. Facing these difficulties the development of ground based techniques becomes necessary. The use of centrifugation to produce hypergravity is potentially a useful tool to detect the critical periods, provided that a careful attention is given to the expected criteria to detect a critical period when the stimulus if amplified instead of removed. In addition, a standardization of the centrifugation techniques should be desirable. On the other hand the use vestibular deficient mutated mice proved to be useful, and the availability of conditioned KO is a promising tool for the future.

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Visual gravitational motion and the vestibular system in humans

***Francesco Lacquaniti*[1,2,3] *, *Gianfranco Bosco*[1,2,3], *Iole Indovina*[2,3], *Barbara La Scaleia*[3], *Vincenzo Maffei*[3], *Alessandro Moscatelli*[4] *and Myrka Zago*[3]**

[1] *Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy*
[2] *Centre of Space Bio-medicine, University of Rome Tor Vergata, Rome, Italy*
[3] *Laboratory of Neuromotor Physiology, IRCCS Santa Lucia Foundation, Rome, Italy*
[4] *Department of Cognitive Neuroscience, University of Bielefeld, Bielefeld, Germany*

Edited by:
Christophe Lopez, Centre National de La Recherche Scientifique, France

Reviewed by:
Hugo Merchant, Universidad Nacional Autónoma de México, Mexico
Dan M. Merfeld, Mass Eye and Ear, USA

***Correspondence:**
Francesco Lacquaniti, Centre of Space Bio-medicine, University of Rome Tor Vergata, Via Montpellier 1, 00133 Rome, Italy; Laboratory of Neuromotor Physiology, IRCCS Santa Lucia Foundation, Via Ardeatina 306, 00178 Rome, Italy
e-mail: lacquaniti@med.uniroma2.it

The visual system is poorly sensitive to arbitrary accelerations, but accurately detects the effects of gravity on a target motion. Here we review behavioral and neuroimaging data about the neural mechanisms for dealing with object motion and egomotion under gravity. The results from several experiments show that the visual estimates of a target motion under gravity depend on the combination of a prior of gravity effects with on-line visual signals on target position and velocity. These estimates are affected by vestibular inputs, and are encoded in a visual-vestibular network whose core regions lie within or around the Sylvian fissure, and are represented by the posterior insula/retroinsula/temporo-parietal junction. This network responds both to target motions coherent with gravity and to vestibular caloric stimulation in human fMRI studies. Transient inactivation of the temporo-parietal junction selectively disrupts the interception of targets accelerated by gravity.

Keywords: internal model, interception, microgravity, time perception, insula, temporo-parietal junction, self-motion

INTRODUCTION

Humans as well as other animals very often experience the vision of objects accelerated by Earth gravity, such as objects in free-fall, projectile, or pendulum motion. Also self-motion may involve an optic flow accelerated by gravity, as when falling or jumping from a height. Whether an object is moving (object-motion), we are moving (self-motion) or both are moving, we must be able to predict the future trajectory of the target to bring about desirable collisions (making interceptions), avoid unwanted collisions or simply anticipate the future course of an event we are watching. Indeed, survival of animals in the forest often depends on accurate estimates of flight time for either self-motion or object motion. Thus, a predator jumping off a tree must time its flight to grab a prey on the spot, while the prey must time the escape from the predator to avoid being caught. Humans are more often engaged in less dangerous but equally demanding tasks, as when they practice sports such as down-hill skiing, trampoline jump or diving, all of which involve gravitational self-motion. Gravitational object motion is experienced, for instance, when we try to save an object which has slipped through our fingers. Also, watching or playing many recreational or sport activities involve the predictive estimate of the movement time of a flying ball.

Predicting the vertical component of target motion under gravity (neglecting air drag) is equivalent to solving the equations:

$$x(t+\Delta t) = x(t) + \dot{x}(t)\Delta t - 0.5g\Delta t^2$$

$$\dot{x}(t+\Delta t) = \dot{x}(t) - g\Delta t$$

$x(t)$ and $\dot{x}(t)$are the vertical position and speed of the target at a given time t, while $x(t+\Delta t)$ and $\dot{x}(t+\Delta t)$are the position and speed after a Δt time interval, and g is the acceleration due to gravity (about 9.8 m s^{-2}). In other words, the model equations extrapolate current position and speed of the target Δt in the future. Our brain presumably does not solve the equations explicitly, but it must extrapolate target trajectory one way or another in order to compensate for the intrinsic delays in processing sensory and motor information. Without extrapolation, the neural estimates of position and speed of a visual target at a given instant of time would correspond to values sometime in the near past, and we would intercept or avoid collision at a place where the target used to be, rather than where the target currently is (Nijhawan, 2008).

Delays cumulate as information is processed during the visuo-motor transformations leading to a response. Thus, neural responses in the middle-temporal (MT) area of the monkey (a critical region for visual motion processing) lag by about 50 ms behind the changes in target speed (Lisberger and Movshon, 1999; Krekelberg, 2008). It takes at least another 100–150 ms to translate these neural visual signals into an overt motor response (such as that involved in reaching and catching), resulting in a net visuo-motor delay of about 150–200 ms (Zago et al., 2008, 2009; Vishton et al., 2010). On-going visual information for a moving target may be updated faster than for the sudden appearance of a stimulus, but overall visuo-motor delays can hardly fall below about 110 ms (Brenner and Smeets, 1997; Zago et al., 2008, 2009).

A correct extrapolation relies on an estimate of the gravitational acceleration g. However, the visual system does not have direct

access to the absolute *g*, but only to the corresponding retinal image information (Regan, 1997). Whereas *g* is constant at a given location, the acceleration of the resulting image on the retina is not constant at all, but varies inversely with viewing distance. The problem is that the visual system is quite poor at estimating image accelerations (Werkhoven et al., 1992; Dessing and Craig, 2010), as is the oculomotor pursuit system in tracking accelerated targets (Watamaniuk and Heinen, 2003; Bennett and Benguigui, 2013). Nevertheless, visual perception (Moscatelli and Lacquaniti, 2011; Indovina et al., 2013a) and manual interception of targets accelerated by gravity can be very precise (Lacquaniti and Maioli, 1987, 1989; Zago et al., 2004, 2008, 2009; Vishton et al., 2010). It follows that the brain must rely on some trick to supplement on-line visual signals in order to take into account the effects of gravity on object motion or self-motion.

One hypothesis is that the effects of gravity are taken into account by combining multisensory information with *a priori* information about the direction and magnitude of the gravity vector, resulting in an internal model able to predict target motion under gravity (Zago et al., 2004; Indovina et al., 2005; Zago and Lacquaniti, 2005a,c). (An internal model is a neural process that mimics a physical event, see Kawato, 1999; Merfeld et al., 1999) According to this hypothesis, the internal model of gravity effects is used to tune motor responses or perceptual judgments of visual gravitational motion. The vestibular system integrates multisensory information, including vestibular, visual and proprioceptive cues (Fukushima, 1997; Lopez and Blanke, 2011), and represents the prime system for providing gravity-related signals. Here we describe behavioral and neural responses to visual gravitational motion, and we consider putative mechanisms for processing gravity effects on a target motion. Studies of object motion are reviewed first, followed by studies of self-motion.

OBJECT MOTION

BEHAVIORAL RESPONSES

There is ample behavioral evidence that Earth's gravity is taken into account in several forms of implicit knowledge, including visual perception or memory of object-motion. Thus, gravity is taken into account when judging the duration of motion of a falling target (Grealy et al., 2004; Huber and Krist, 2004; Brouwer et al., 2006; Moscatelli and Lacquaniti, 2011). Moreover, the final position of a horizontally moving target (Hubbard, 1995) or a projectile (De Sá Teixeira et al., 2013) that are suddenly halted is misremembered as being displaced downward below the path of motion, consistent with the idea that gravity effects are implicitly assumed by the observers. The oscillations of a pendulum represent another familiar example of gravitational motion. Visual perception is sensitive to deviations from the relation between pendulum period and pendulum length (Bozzi, 1958; Pittenger, 1990; Frick et al., 2005). Indeed, in experiments in which a pendulum oscillates faster or slower than normal, the observers rate the oscillations violating the physical length-period relation less natural than those complying with physics (Pittenger, 1990).

The largest body of evidence for an internal model of gravity effects on target motion has been accumulated in studies of manual interception of a falling object (Zago and Lacquaniti, 2005a,c; Zago et al., 2008, 2009). Depending on the specific protocol, interception could involve catching (Lacquaniti and Maioli, 1987, 1989; Lacquaniti et al., 1993; Vishton et al., 2010), punching (Zago et al., 2004, 2005; Zago and Lacquaniti, 2005b) or batting (Katsumata and Russell, 2012) a ball dropped vertically. In all cases, the movements were well synchronized with the arrival of the ball. In particular, anticipatory electromyographic (EMG) responses in upper limb muscles were roughly time-locked to the expected arrival of the ball, independent of the height of fall when this was changed from trial to trial (Lacquaniti and Maioli, 1987, 1989).

A similar anticipatory activity has been described for manual catching of a ball thrown in projectile motion (Savelsbergh et al., 1992; Cesqui et al., 2012; D'Andola et al., 2013). Gravity effects appear to be taken into account also in the oculomotor behavior necessary to track projectile motion (Diaz et al., 2013). Gómez and López-Moliner (2013) recently showed that knowledge of absolute target size (s) and gravity (g), combined with signals about optical size of the target (visual angle θ), its elevation angle (γ) and time derivative ($\dot{\gamma}$), can provide reliable estimates of projectile motion in 3D. The corresponding time-to-contact (TTC) estimate for interception is defined by:

$$TTC = \frac{2s\dot{\gamma}}{g\theta \cos \gamma}$$

While target size and gravity are constants related to the context, optical size, elevation angle and its time derivative are time-varying variables derived from on-line visual information.

Predictive behavior related to the anticipation of gravity effects has also been revealed by occluding the terminal phase of target motion (Dessing et al., 2009; Zago et al., 2010; Baurès and Hecht, 2011; Bosco et al., 2012; Katsumata and Russell, 2012) or by stopping target motion unexpectedly before arrival (Vishton et al., 2010).

The bulk of the studies cited above show that TTC estimates for motions accelerated by gravity take into account target acceleration. Gravity is such a strong acceleration that estimates neglecting it would lead to considerable timing errors, especially over relatively short heights of target fall (Tresilian, 1999; Zago et al., 2008). This contrasts with many interceptive or avoidance tasks which involve motion not affected by gravity, such as horizontal motion. Horizontal motion is often uniform (at constant speed) or accelerations are so modest to be safely neglected. Indeed, there is much experimental evidence that first-order estimates based on optical variables related to position and velocity are used to accurately predict the TTC for targets moving along the horizontal (Lee, 1976; Tresilian, 1999; Regan and Gray, 2000; Zago et al., 2009). One such optical variable that has received special attention is represented by tau, defined as the ratio between image size and its rate of change (Lee, 1976). Tau can provide a direct estimate of TTC for a target approaching at constant speed the observer along the sightline, with no need to estimate the object's distance and speed relative to the eye, nor the object's absolute size.

Performance in weightlessness

In contrast with the accurate performance associated with targets accelerated by Earth gravity, the interception performance with targets descending vertically at constant speed ($0g$) is often inaccurate, movements being timed too early. Real $0g$ (weightless)

conditions were tested in astronauts during orbital flight (McIntyre et al., 2001), while 0*g*-motion of a visual target was simulated in the laboratory (Zago et al., 2004, 2005; Zago and Lacquaniti, 2005b). The timing errors are striking, because motion at constant speed can be measured reliably by the visual system (McKee et al., 1986; de Bruyn and Orban, 1988; Werkhoven et al., 1992), and first-order TTC estimates are successfully used in case of horizontal motion, as noticed above. Therefore, if subjects relied entirely on visual feedback, with practice they should be able to intercept 0*g* targets descending vertically, just as they do with horizontally moving targets. Instead, the persistence of timing errors observed even after 14 days in orbit is consistent with the operation of an internal model which assumes that descending targets are always accelerated by Earth gravity (Lacquaniti et al., 1993; Tresilian, 1999; McIntyre et al., 2001; Zago and Lacquaniti, 2005b).

Role of vestibular signals

A series of studies showed that vestibular signals detecting the direction of gravity can be used to tune motor behavior in response to visual gravitational motion. Senot et al. (2005) asked subjects to intercept a ball approaching in a virtual scene presented stereoscopically in a head-mounted stereoscopic display. Subjects either pitched their head backward so as to look up toward the ball falling from a ceiling, or they pitched their head downward so as to look toward the ball rising from a floor. The visual reference frame for up and down was anchored to the physical gravitational vertical, as sensed by the vestibular system. It was found that subjects were more accurate at intercepting targets whose motion obeys gravity (accelerating while they descend from above and decelerating while they ascend from below), rather than targets whose motion violates gravity (decelerating while descending and accelerating while ascending). This fits with the idea that interception timing depends on gravity-related information (Senot et al., 2005; Le Séac'h et al., 2010). In particular, because otolith sensory organs respond differently according to the orientation of the head with respect to gravity (Fernandez and Goldberg, 1976), they help defining the direction of expected gravity acceleration.

Consistent with this hypothesis, a study performed during a parabolic flight campaign provided evidence for a contribution of otolith sensors in the visuomotor responses to accelerating/decelerating targets (Senot et al., 2012). During each parabola, a 20-s weightless (0*g*) phase is preceded and followed by 20-s of hypergravity (1.5–1.8*g*). The unloading of the otoliths when passing from hypergravity to hypogravity is sensed as a negative gravity, i.e., as a gravitational pull in the upward direction. Strikingly, the timing of the interceptive responses in the virtual environment described above (Senot et al., 2005) reversed sign during the weightless phases compared with the responses at normal gravity (Senot et al., 2012). This reversal, therefore, can be attributed to a corresponding reversal of the otolith responses during the transition from hypergravity to hypogravity.

Virtual gravity defined by visual cues

An up/down reference can be strongly biased by contextual cues included in the visual scene. Indeed, as mentioned above, astronauts continued to anticipate the effects of Earth gravity on a ball projected "downward" from the ceiling of the space shuttle (McIntyre et al., 2001). On Earth, the effects of a virtual gravity in a visual scene with strong up/down cues are anticipated even when the target moves in a head-to-feet direction of supine subjects (Miller et al., 2008) or in an oblique direction of seated subjects (Moscatelli and Lacquaniti, 2011).

Not only can pictorial cues affect the perception of gravity direction, but they also contribute mapping between retinal and world information and calibrating the effects of gravity on a visual target by providing a perspective metric (Zago et al., 2009). In order to process visual gravitational motion, the brain must combine target motion, which is represented topographically on the retina, with an internal representation of gravity, which is presumably specified in the world coordinates of the visual scene. This combination requires making reference to a common spatial frame. Retinal motion information might be scaled by the viewing distance to estimate target motion in world coordinates. Eye vergence, accommodation and stereo-disparity may contribute to estimating viewing distance of target motion in 3D space, but these cues are ineffective when the target is far or when it moves on a 2D video display (as in a videogame). Pictorial information such as that provided by natural objects in the visual scene also aids recovery of an environmental reference and scale (Distler et al., 2000). For instance, if an object fell near a person, the estimated height of the person can be used to scale the motion of the falling object, effectively recovering the apparent distance from the viewer (Miller et al., 2008). Indeed, consistent with the idea that pictorial information about the scale of the scene helps calibrating the effects of gravity, when such pictorial information is missing, the interception performance with targets accelerated by gravity is considerably worse than in the presence of pictorial information (Miller et al., 2008).

Zago et al. (2011a) manipulated the alignment of virtual gravity and structural visual cues between each other, and relative to the orientation of the observer and physical gravity. A factorial design assessed the effects of the scene orientation (normal or inverted) and the direction (normal or inverted) of virtual gravity affecting target motion. It was found that interception was significantly more successful when scene direction was concordant with target gravity direction, irrespective of whether both were upright or inverted. These results show that the visible influence of virtual gravity and pictorial cues can outweigh both physical gravity and viewer-centered cues, leading to rely instead on the congruence of the apparent physical forces acting on people and objects in the scene. In another study, it was shown that the presence of biological movements in animate scenes helps processing target kinematics under the ecological conditions of coherence between scene and target gravity directions (Zago et al., 2011b). In this study, button-presses triggered the motion of a bullet, a piston, or a human avatar (animated with actually recorded biological motion) that intercepted the moving target. The timing errors were smaller with the human avatar than the bullet or piston, but only when the directions of scene and target gravity were concordant.

Combination of cues

Estimates of the direction of gravity effects on a target motion generally depend on a combination of multiple cues. Such a combination was revealed in the study by Moscatelli and Lacquaniti

(2011) who asked observers to judge the duration of motion of a target accelerating in one of four different directions, downward, upward, leftward and rightward relative to a visual scene. Downward motion complied with the gravity constraint, whereas motion in the other directions violated this constraint. Observers watched either a pictorial or a blank scene, while being upright or tilted by 45° relative to the monitor and Earth's gravity. In another condition, observers were upright and the scene was tilted by 45°. It was found that discrimination precision (inversely related to response variability) was better for downward motion than for the other directions, consistent with the action of visual gravity. However, the difference in precision was not constant across conditions, but was highest when both the observer and the pictorial scene were upright and lowest when the target direction in the non-pictorial scene was tilted by 45° relative to an upright observer. To model the graded behavior across conditions, Moscatelli and Lacquaniti (2011) used a linear combination of the three types of cues experimentally manipulated. They found that pictorial cues accounted for 43% of the overall response, orientation of the observer relative to the physical vertical accounted for 37% of the response, and orientation of target motion relative to the physical vertical accounted for the remaining 20%. Similarly, De Vrijer et al. (2008) suggested an ideal observer model for motion percept based on a linear combination of vestibular and visual cues, each cue being weighed as a function of its reliability.

The relevance of egocentric cues specifying the observer's orientation is in line with much previous work on the perceptual discrimination of scenes, people and actions (e.g., Troje, 2003; Kushiro et al., 2007; Chang et al., 2010). On the other hand, the substantial contribution of visual references intrinsic to the scene, such as the direction of target motion and the presence of pictorial cues, agrees with the observation that viewing a photograph with strong polarization cues indicating relative up and down directions in the picture can alter the perceived direction of the vertical in the real world (Jenkin et al., 2004).

The ability to discriminate upright objects relative to tilted ones is critical, in so far as upright objects tend to be stable while tilted objects may fall down. Lopez et al. (2009) assessed perceptual judgments of the stability (tendency to fall) of pictures of a human figurine with implied motion. They found combination of cues, because judgments are affected by the picture's orientation with respect to the physical gravity, the participant's body, and the pictorial gravity embedded in the figurine for directions that are not concordant with the direction of physical gravity.

In sum, spatial representations for the effects of gravity on a target motion are presumably flexible, and can be biased by different egocentric and allocentric references depending on the context and the available cues. This view agrees with the hypothesis that neural estimates of gravity direction are computed by the Central Nervous System as a Bayesian weighted average of multi-cue information, including vestibular, visual, neck and truncal signals, plus a prior distribution about head and body orientation (Van Beuzekom and Van Gisbergen, 2000; Zupan et al., 2002; MacNeilage et al., 2007; De Vrijer et al., 2008). As far as the vestibular signals are concerned, the otoliths cannot distinguish gravity from linear acceleration (according to Einstein's Equivalence Principle), but measure specific gravito-inertial force (vector sum of gravity minus linear acceleration). However, the vestibular system is able to estimate the gravity vector in head coordinates by combining signals from otoliths and semicircular canals (Merfeld et al., 1999, 2005). Thus, head orientation relative to gravity can be estimated by integrating the vector cross-product of the estimated angular head velocity (derived from canal inputs) and the direction of gravity (derived from otolith inputs).

NEURAL SUBSTRATES

The hypothesis that the effects of gravity on a target motion are taken into account by combining multisensory information, including visual and vestibular cues, is supported by neuroimaging studies. Senot et al. (2008) used magneto-encephalography (MEG) during hand catches of a real free-falling ball. MEG revealed the temporal dynamics of activation, by showing that peaks of brain activity are evoked in posterior occipital and lateral parieto-temporal regions about 80–100 ms after ball release, and propagate to sensori-motor cortex in about 40 ms. While MEG affords excellent temporal resolution of the neural events, it lacks the spatial accuracy and resolution necessary to localize the activity peaks at specific brain sites. This spatial localization was provided by a series of fMRI studies that employed computer animations of a target moving up and down along a visual vertical defined by context cues (Indovina et al., 2005; Miller et al., 2008; Maffei et al., 2010). The visual vertical was aligned with the physical vertical in Indovina et al. (2005), while it was orthogonal to it and aligned with the subject's body in Maffei et al. (2010) and Miller et al. (2008). The target could move under gravity (1*g*, decelerating on the way up and accelerating on the way down) or under artificial, reversed gravity ($-1g$, accelerating going up and decelerating coming down). As expected, the comparison of both types of target motion with a no-motion baseline showed activation in an occipital-temporo-parietal network largely overlapping with the classical dorsal stream for visual motion processing (Orban et al., 2003), including early visual areas (human homologs of monkey V1, V2, V3), hMT/V5+, and intra-parietal sulcus (IPS) areas.

Network for object motion under gravity

In the fMRI studies listed above, 1*g* (natural gravity) trials were associated with significantly greater activity than $-1g$ (reversed gravity) trials in a network of regions located within and around the Sylvian fissure close to the temporo-parietal junction (TPJ): posterior insular cortex, retro-insula, parietal operculum, supramarginal gyrus, temporal operculum, superior and middle temporal gyri (**Figure 1**). In addition, 1*g* trials engaged sensorimotor cortex including primary somatosensory and motor cortex, ventral premotor cortex, SMA, cingulate cortex, visual cortex including the lingual gyrus, and several subcortical structures including posterior thalamus, putamen, cerebellum and vestibular nuclei (**Figures 1,2**).

An involvement of sensorimotor cortex, SMA, basal ganglia and cerebellum may not be specific of gravity-related motion, but may depend on the temporal prediction of a forthcoming collision, which is more accurate for 1*g* than $-1g$ trials. Indeed, a similar engagement of some of these regions is observed in tasks which require perceptual judgments of TTC of targets moving at constant speed, perhaps based on the optical variable tau (Field and Wann,

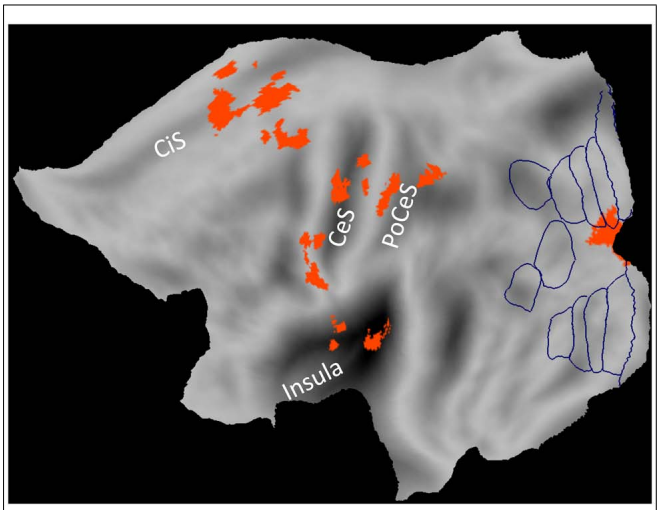


FIGURE 1 | Brain responses to vertical object motion under gravity. Statistical parametric maps of the main effect of 1 g motion (data from Indovina et al., 2005) projected on a flat map of the left hemisphere of the human PALS atlas (Caret). Activations correspond to greater blood-oxygen-level-dependent response to vertical motion compatible with gravity (1*g*) than motion incompatible with gravity (−1*g*). Boundaries of visual areas derived from Caret are traced in blue. CeS, central sulcus; CiS, cingulate sulcus; PoCeS, post-central sulcus.

2005, **Figure 3**). In the monkey, neural discharge in area 7a of the parietal cortex and in primary motor cortex is related to various parameters of stimulus motion, including TTC based on first-order optical cues (Merchant et al., 2004; Merchant et al., 2009).

Instead, the involvement of peri-Sylvian regions close to TPJ appears to be specific of object motion under gravity. Moreover, the neural preference for visual gravitational motion in these regions holds irrespective of the specific spatio-temporal properties of the visual stimulus. Maffei et al. (2010) asked subjects to intercept 1*g* and −1*g* targets either in smooth motion or in long-range apparent motion (LAM, Braddick, 1980). LAM was generated by flashing stationary targets in sequence at different locations along the vertical path, with a wide spatial and temporal separation. Both the insula and lingual gyrus were significantly more active during 1*g* than during −1*g* trials in both real and apparent motion conditions. A region in the inferior parietal lobule showed a preference for 1*g* only during apparent motion but not real motion.

Bosco et al. (2008) transiently disrupted the activity of TPJ or hMT/V5+ by means of trans-cranial magnetic stimulation (TMS), while subjects pressed a button to intercept targets moving at 1 or −1*g* in the vertical or horizontal direction. They found that TMS of hMT/V5+ affected the interception timing for all tested motion types, whereas TMS of TPJ affected only the interception timing of motion coherent with gravity, that is 1*g* vertical motion (**Figure 4**). Thus, TMS perturbations showed a causal relationship between the activity of TPJ and the processing of visual gravitational motion.

We mentioned above that pictorial information provided by natural objects in the visual scene helps recovering an environmental reference and scale. An fMRI study (Miller et al., 2008) revealed correlates of these visual context effects on gravitational motion processing at a surprisingly early stage of visual-vestibular processing, that is, in the vestibular nuclei and posterior cerebellar vermis (**Figure 2**). In sum, the studies reviewed above indicate that the effects of gravity on object motion are represented in a highly distributed cortical-subcortical network. In a following section, we will show that a similar distributed network underlies the processing of gravity effects during self-motion.

Co-localization with the vestibular network

Indovina et al. (2005) found that several of the brain sites responding to 1*g* visual stimuli co-localized with the regions independently activated by vestibular caloric stimuli. They then concluded that these regions were presumably identifiable as belonging to the multi-modal visual-vestibular network (**Figure 5**). In fact, posterior insula, retroinsular cortex, and parietal operculum at TPJ possibly represent the human functional equivalent (Brandt and Dieterich, 1999) of the parieto-insular vestibular cortex of the monkey, the core region of vestibular cortex described by Guldin and Grüsser (1998). Indeed, a meta-analysis of 16 human neuroimaging studies using caloric, galvanic, or acoustic stimulation of vestibular receptors shows activation of these regions (Lopez et al., 2012). This meta-analysis was based on a robust activation-likelihood-estimation. The largest clusters of activation were found in the Sylvian fissure, at the level of the insula and retroinsular region, as well as at the temporal and parietal banks of the Sylvian fissure (Lopez et al., 2012; see also zu Eulenburg et al., 2012). The borders of the regions activated by vestibular caloric stimuli derived from the meta-analysis are plotted in the flat map of **Figure 5**. It can be seen that several foci of activation reported in different studies in response to visual gravitational motion (colored dots in **Figure 5**) fall within these borders.

Notice that several of the regions which respond to vestibular stimuli are truly multimodal, because they also respond to optic flow and neck proprioceptive stimuli in human neuroimaging studies (Bense et al., 2001; Bottini et al., 2001; de Waele et al., 2001; Dieterich et al., 2003a,b). Vestibular cortical regions receive di-synaptic inputs from the vestibular nuclei complex via the posterior thalamus (Guldin and Grüsser, 1998; de Waele et al., 2001; Lopez and Blanke, 2011). Lesions of vestibular cortex can lead to a tilt of the perceived visual vertical and rotational vertigo/unsteadiness (Brandt and Dieterich, 1999). A recent clinical report shows that lesions restricted to the posterior insular cortex do not involve vestibular deficits, suggesting that these lesions have to be combined with lesions of adjacent regions of the cortical and subcortical vestibular network to cause vestibular otolith deficits (Baier et al., 2013). Focal electrical stimulation or epileptic discharges around TPJ can elicit sensations of self-motion or altered gravity (Blanke et al., 2002; Isnard et al., 2004; Nguyen et al., 2009). In the monkey, in addition to the vestibular cortex (Guldin and Grüsser, 1998), early visual areas (V2 and V3/V3a) show combined effects of visual and otolith information (Sauvan and Peterhans, 1999). These visual areas might be a functional homolog of the site in the lingual gyrus that is activated by 1*g* trials in human fMRI (Maffei et al., 2010).

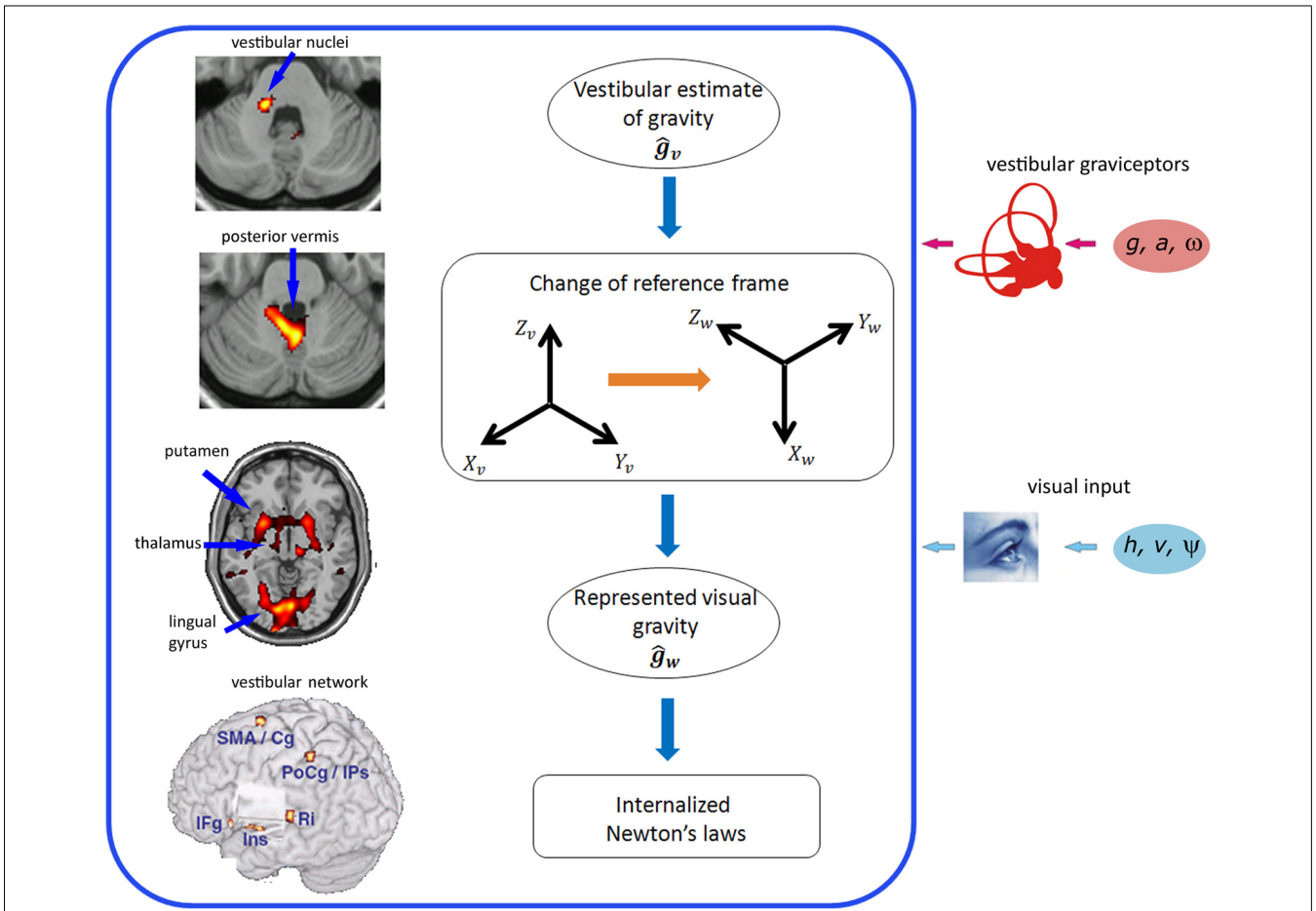


FIGURE 2 | Brain network (left) and neural computations (right) for processing visual gravitational motion. Left (top to bottom): activations in vestibular nuclei in the brainstem, posterior cerebellar vermis, putamen, thalamus, lingual gyrus, and overall cortical network of common activations for visual 1*g* motion and caloric vestibular stimulation (peri-sylvian volume removed to show the insular region, deep in the Sylvian fissure). Ins, insula; Ri, retro-insula; IFg, inferior frontal gyrus; PrCg, pre-central gyrus; SMA, supplementary motor area; Cg, middle cingulate gyrus; PoCg, post-central gyrus; IPs, intra-parietal sulcus; SMg, supramarginal gyrus; STg, superior temporal gyrus. Right (top to bottom): The vestibular semicircular canals measure the angular velocity of the head (ω), while the otolith organs measure both gravity (*g*) and linear acceleration of the head (*a*). Internal model calculations are included within the box. A vestibular estimate of gravity ($\hat{g}_V$) is computed in head-fixed coordinates (X_V, Y_V, Z_V) by the Central Nervous System. Rotational optokinetic cues (ψ) and extra-vestibular graviceptive cues may also contribute toward computing $\hat{g}_V$. An abstract representation of gravity ($\hat{g}_W$) accessible by the visual system is constructed by a change of reference frame to world-fixed coordinates (X_W, Y_W, Z_W), so that it matches the perceived top-bottom axis (Z_W) of the visual scene. The internal model of Newton's laws results from the combination of $\hat{g}_W$ with on-line visual estimates about target motion (*h* and *v* are the vertical position and velocity of the target, respectively), and can be used by the brain for different scopes, such as predicting target TTC, or perceiving a motion as natural. fMRI data in the left are modified with permission from Miller et al. (2008) and Indovina et al. (2005). Neural computations are modified with permission from Indovina et al. (2005).

SELF-MOTION

BEHAVIORAL RESPONSES

Visual perception of heading direction during self-motion relies on multiple cues, including optic flow, monocular or stereo depth, and path (e.g., Duffy and Wurtz, 1991; Warren, 2006; Merchant et al., 2009). The visual effects of gravity may also contribute to heading perception. Vidal et al. (2006) tested the ability to perceive and remember self-motion when subjects are driven passively at constant speed through virtual 3D tunnels that curve in different directions (up, down, left, right). When subjects indicated the amplitude of the turn, they showed a significant asymmetry in pitch-induced perception: downward stimuli produced a stronger pitch perception than upward stimuli, while leftward and rightward yaw turns were perceived equally (Vidal et al., 2006). A subsequent study with the same protocol performed during long-duration space flight aboard the International Space Station showed that weightlessness alters up/down asymmetries in the perception of self-motion (De Saedeleer et al., 2013). Vestibular versus haptic cues were manipulated by having cosmonauts perform the task either in a rigidly fixed posture with respect to the space station or during free-floating. The asymmetry between downward and upward pitch turns observed on Earth showed an immediate reduction when the cosmonauts were free-floating, and a delayed reduction when they were firmly in contact with the floor of the station. Thus, the lack of graviceptive inputs in weightlessness alters the processing underlying the visual perception of

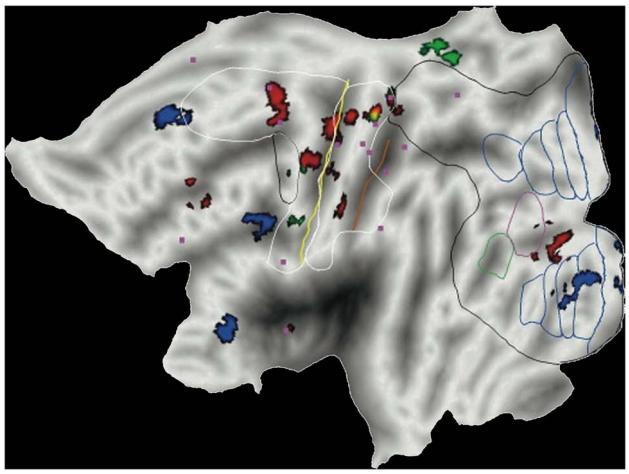


FIGURE 3 | Brain responses in time-to-contact estimates unrelated to gravity. In the TTC task, observers decided which of two approaching objects would arrive first. In the inflation task IJ, observers judged which object was expanding faster. In the gap closure task GC, observers judged which of two remote objects translating in the frontoparallel plane would arrive first at a central target location. Activation for the contrast TTC – IJ is shown in red, GC – IJ in green, and IJ – TTC in blue (Reproduced with permission from Field and Wann, 2005.)

self-motion. The finding that the effects on pitch perception are partially overcome by haptic cues indicates the fusion of multisensory (visual, tactile, proprioceptive) cues and top-down cognitive influences.

A different issue concerns the role of visual kinematics during self-motion along the cardinal directions, horizontal and vertical. These directions are typically cued by the orientation of several features of the scene, such as the horizon, trees, buildings, or people. Moreover, kinematics often differs between vertical and horizontal self-motion. Thus, during steady motion, we are typically displaced horizontally at a roughly constant speed, whereas we fall downward and move upward under gravity in an accelerated and decelerated manner, respectively.

Visual estimates of time-to-passage during passive self-motion along the cardinal directions have been reported by Indovina et al. (2013a). Subjects experienced virtual rides on a roller-coaster in a first-person perspective compatible with forward self-motion (Baumgartner et al., 2008). The car traveled along tracks consisting of separate vertical and horizontal rectilinear sections, connected by curves. In both vertical and horizontal sections, the car accelerated, decelerated, or moved at constant speed. Car acceleration/deceleration was coherent with gravity for vertical motion, while the same acceleration/deceleration was rather artificial for horizontal motion. These visual stimuli provide an

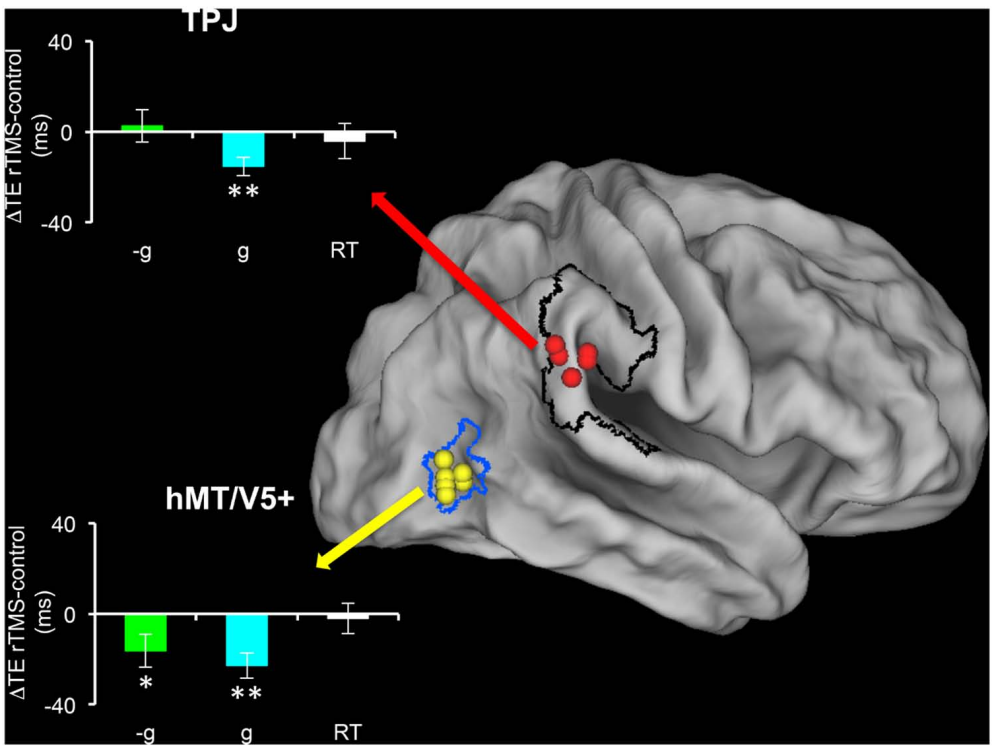


FIGURE 4 | Effects of repetitive transcranial magnetic stimulation (rTMS) of TPJ and hMT/V5+ on the interception of targets descending along the vertical with natural (1*g*) or artificial (−1*g*) acceleration (modified with permission from Bosco et al., 2008). Individual TMS sites in TPJ (red) and hMT/V5+ (yellow) are mapped on the Caret PALS human brain (slightly inflated). hMT/V5+ borders (blue) are derived from the probabilistic map of Malikovic et al. (2007), while the black contour delimits the perisylvian region (including TPJ) activated by vestibular caloric stimulation in Indovina et al. (2005). Bar graphs show the mean timing differences (±SEM) between post-rTMS and pre-rTMS interceptive responses. Cyan, 1*g* targets; green, −1*g* targets; white, simple reaction time task, which controlled for specificity of rTMS effects. *$p < 0.05$; **$p < 0.001$ (repeated-measures ANOVA).

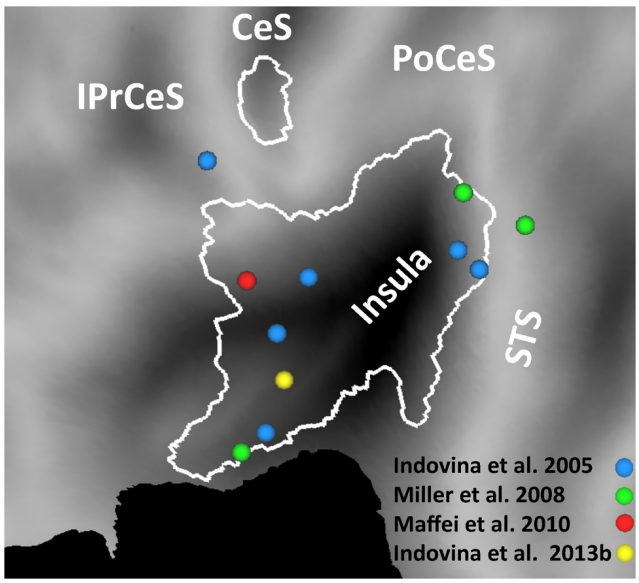


FIGURE 5 | Brain responses to visual gravitational motion and responses to vestibular stimuli projected on a flat map of the left hemisphere of the human PALS atlas (Caret) to show activations in the Sylvian fissure. Colored dots denote peaks of activity measured in fMRI studies of visual object motion (cyan, Indovina et al., 2005; green, Miller et al., 2008; red, Maffei et al., 2010) and self-motion (yellow, Indovina et al., 2013b). The peaks identify brain sites showing significantly greater blood-oxygen-level-dependent response to vertical motion compatible with gravity than motion incompatible with gravity. White contours demarcate the borders of regions identified by means of meta-analysis of vestibular caloric studies (with permission from Lopez et al., 2012). CeS, central sulcus; IPrCeS, inferior pre-central sulcus; PoCeS, post-central sulcus; STS, superior temporal sulcus.

immersive sense of presence in the virtual environment (Baumgartner et al., 2008), and elicit comparable self-motion sensations across vertical and horizontal paths (Indovina et al., 2013a,b). Subjects were required to press a button when they thought the rollercoaster would pass through a reference point in the scene. In a separate experiment, no visual information was provided during the final part of the path to eliminate the possibility of response triggering upon detection of a given proximity to the target. It was found that, for both visible and occluded conditions, acceleration (positive or negative) was taken into account, but was somewhat overestimated in the calculation of time-to-passage, independently of orientation. Moreover, observers signaled time-to-passage earlier when the rollercoaster accelerated downward at 1*g* (as during free fall), with respect to when the same acceleration occurred along the horizontal orientation. This time shift indicates an influence of the orientation relative to visual gravity due to the anticipation of the effects of gravity on self-motion along the vertical, but not the horizontal orientation. During vertical self-motion, the precision in time-to-passage estimates was higher during accelerated falls than when traveling at constant speed, consistent with a lower noise in time-to-passage estimates when the motion complies with the gravity constraint as compared to when the motion violates the constraint.

NEURAL SUBSTRATES

The neural correlates of passive self-motion in the rollercoaster have been investigated by Indovina et al. (2013b) by using fMRI. Vertical self-motion coherent with gravity engaged the posterior insula, ventral premotor cortex, pre-SMA, cingulate cortex, thalamus, dorsal striatum, cerebellar cortex, and vermis (**Figure 6**). These brain regions, but most systematically the posterior insula, have been previously associated with vertical object motion under gravity (Indovina et al., 2005; Miller et al., 2008; Maffei et al., 2010). During self-motion, the retina is specifically activated by the optic flow, and these inputs related to the directional velocity of the image on the retina are relayed via the nuclei of the optic tract and reticularis tegmenti pontis to the vestibular nuclei and the cerebellum and then forwarded to the vestibular cortical network where processing related to the self-motion percept probably occurs.

In the experiments by Indovina et al. (2013b), gravity-related visual kinematics could be extracted from motion signals, by matching the stimuli with a reference gravity template. However, the activation of the posterior insula did not depend on optic flow imbalance between different kinematics. Indeed, it was observed also in a separate experiment where all visual cues (including optic flow) were identical between vertical and horizontal sections. This was obtained by presenting rectilinear motion within dark tunnels, whose direction was cued only by the preceding open-air curves.

Previous fMRI studies reported inconsistent responses of the insula and TPJ (including the retroinsula) to optic flow, with either

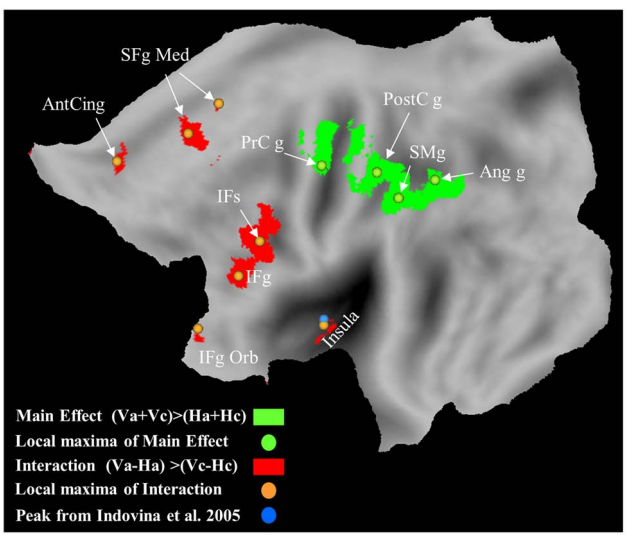


FIGURE 6 | Brain responses with vertical self-motion compatible with gravity, and with vertical motion independent of motion law. Statistical parametric maps for the interaction of motion direction by motion law, and maps for the main effect of vertical motion direction are plotted in red and green, respectively. Orange and green dots represent the local maxima for the interaction and main effect, respectively. Cyan dot represents the average maximum in the left posterior insula for vertical object motion coherent with gravity (Indovina et al., 2005). Ant Cing g, anterior cingulate gyrus; IFg, inferior frontal gyrus; IFg Orb, inferior frontal gyrus pars orbitalis; IFs, inferior frontal sulcus; PrCg, pre-central gyrus; PostCg, post-central gyrus; SFg Med, superior frontal gyrus medial; SMg, supra-marginal gyrus.

activations (Antal et al., 2008; Cardin and Smith, 2010) or deactivations (Brandt et al., 1998; Kleinschmidt et al., 2002). Moreover, in a study using 3D vestibular and optic flow stimulation in the monkey (Chen et al., 2010), neurons in the parieto-insular vestibular cortex exhibited robust vestibular responses to both translational and rotational stimuli, but did not respond to optic flow stimulation. Most neurons responding to both sinusoidal rotations and translations are located in the retroinsular cortex. A convergence of signals from the semicircular canals and otoliths in this region as well as the transitional zone with the insular granular field may help disambiguating gravito-inertial forces (see above). Remarkably, a similar convergence could exist also in the human retroinsular cortex, as suggested by the fact that this region is activated by caloric, galvanic and sound stimuli (Lopez et al., 2012).

However, convergence of visual and vestibular inputs related to egomotion has been shown to occur in the monkey visual posterior sylvian area (VPS), which is strongly interconnected to parieto-insular vestibular cortex, as well as in the ventral intraparietal cortex (VIP, Chen et al., 2011a,b). Thus, visual motion regions (such as hMT/V5+, VIP, V6, VPS, and cingulate sulcus visual area) may provide routes for optic flow signals (Smith et al., 2012) to regions such as the posterior insula and the other regions selective for vertical gravitational motion.

The study by Indovina et al. (2013b) further suggested that neural representations of horizontal self-motion are distinct relative to those of vertical self-motion. In fact, unlike vertical motion, horizontal motion engaged medial-temporal regions including para-hippocampus and hippocampus, consistent with their role in inertial navigation (**Figure 7**).

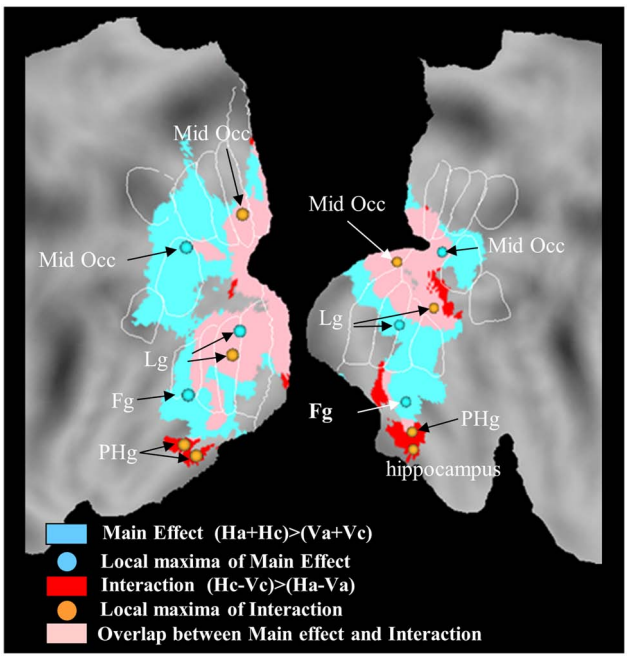


FIGURE 7 | Brain responses with horizontal self-motion at constant speed, and with horizontal motion independent of motion law. Statistical parametric maps for the regions exclusively associated with the interaction of motion direction by motion law are plotted in red, those exclusively associated with the main effect of horizontal motion direction in cyan, and those associated with both the main and the interaction effect in pink. Orange and cyan dots represent the local maxima for the interaction and main effect, respectively. Activations are projected onto flat maps of the left (LH) and right (RH) hemisphere of the human PALS atlas (Caret). Fg, fusiform gyrus; Lg, lingual gyrus; Mid Occ, middle occipital gyrus; PHg, para-hippocampal gyrus.

CONCLUSION

The evidence reviewed above indicates that the visual effects of gravity are taken into account when dealing with both object motion and self-motion. Perceptual judgments as well as motor interactions with targets accelerated by gravity are much more precise than when the targets move with arbitrary accelerations lacking ecological significance. Because the visual system is poorly sensitive to image acceleration, the most likely explanation for how the brain accounts for gravity effects is that it has internalized them.

The internal model can predict target motion under gravity by extrapolating current information about target position and speed into the future. Occlusion studies show that extrapolation can extend well beyond 1 s durations (Baurès and Hecht, 2011; Bosco et al., 2012). However, the neural model does not solve the motion equations exactly, but provides only an approximate estimate of the trajectory. Estimates become quite accurate and precise in the presence of on-line visual feedback, which tends to correct errors arising from imprecision in the model (Zago et al., 2004). Instead, in the absence of visual feedback, timing errors can be substantial (Senot et al., 2005; Zago et al., 2010; Baurès and Hecht, 2011).

The internal model can be construed as a prior expectation about the underlying forces which act on a target. This prior is normally combined with multisensory information, including visual, vestibular, tactile, and proprioceptive cues. The combination may comply with Bayes' law, so that robust sensory evidence for the lack of gravitational acceleration can overrule the prior expectation of Earth gravity, especially when context cues about gravity effects are lacking (Zago et al., 2004, 2010). Formally, the prior is a random variable with the following distribution:

$$\hat{g}_{prior} \approx N(9.81, \sigma^2)$$

The mean of the distribution would be equal to Earth gravitational acceleration, and the variance parameter would account for the variability in the estimate. In Bayesian terms, the posterior estimate is obtained by combining a noisy sensory measurement $\hat{g}_{\text{likelihood}}$ with the prior:

$$\hat{g}_{\text{posterior}} \propto \hat{g}_{\text{likelihood}} \cdot \hat{g}_{\text{prior}}$$

Each term of the second member is weighed inversely to its variance, which measures its reliability. Following a Bayesian interpretation, one would argue that, when the variance in the prior of 1*g* acceleration is very small compared with the variance in the sensory likelihood, the prior prevails, as would be the case of Spacelab experiments or of adaptation experiments with simulated 0*g* targets and context cues about gravity effects (Zago et al.,

2005). In other instances, however, the variance in the prior would be large so that sensory evidence prevails, as would be the case when context cues about gravity effects are weak or absent (Zago et al., 2004). Further experiments involving long-term full immersion in reduced gravity environments are needed to validate the Bayesian hypothesis.

In line of principle, the visual effects of gravity (Calderone and Kaiser, 1989) might be dealt with by the brain independently of vestibular signals. This is because, in contrast with the physical gravity which affects the vestibular receptors, visual gravity effects are not invariant but scale with viewing distance. Moreover, visual gravity may not even be aligned with physical gravity, as when we watch a remote scene on a tilted monitor or in weightlessness. However, there is evidence that vestibular signals modulate behavioral responses to visual gravitational acceleration as shown both on Earth (Senot et al., 2005) and parabolic flight (Senot et al., 2012). Moreover, fMRI experiments showed that several of the neural sites responding to visual gravitational acceleration co-localize with the brain regions responding to direct vestibular stimuli (Indovina et al., 2005). TMS experiments further showed that transient inactivation of TPJ, a key region of the cortical vestibular network, selectively disrupts interception of targets accelerated by gravity (Bosco et al., 2008).

To account for these results, it has been suggested that visual processing of targets accelerated by gravity shares the representation of gravity with the vestibular system (Indovina et al., 2005; Zago and Lacquaniti, 2005c). As we remarked above, a posteriori estimates of gravity orientation and effects would derive by a combination of prior information with visual, vestibular, tactile and proprioceptive cues. We now argue that this combination occurs in a network of regions widely distributed in the brain. **Figure 2** (right panels) presents a conceptual scheme illustrating the neural computations which are hypothetically involved in processing visual gravitational motion. According to this hypothesis, the internal model estimating the effects of gravity on seen objects is constructed by transforming the vestibular estimates of mechanical gravity, which are computed in the brainstem and cerebellum, into internalized estimates of virtual gravity, which are memorized in the vestibular network, including cortical and subcortical regions. The integration of the internal model of gravity with on-line visual signals likely takes place at multiple levels in the cortex. This integration presumably involves recurrent connections between early visual areas engaged in the analysis of spatio-temporal features of the visual stimuli and higher visual areas in temporo-parietal-insular regions involved in multisensory integration. Similarly, also the integration with vestibular, tactile and proprioceptive cues occurs in a distributed brain network.

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A neuroscientific account of how vestibular disorders impair bodily self-consciousness

Christophe Lopez*

Laboratoire de Neurosciences Intégratives et Adaptatives - UMR 7260, Centre Saint Charles, Fédération de Recherche 3C, Centre National de la Recherche Scientifique - Aix-Marseille Université, Marseille, France

Edited by:
Pierre Denise, Université de Caen Basse-Normandie, France

Reviewed by:
John S. Butler, Albert Einstein College of Medicine, USA
Isabella Pasqualini, Ecole Polytechnique Fédérale de Lausanne, Switzerland

****Correspondence:***
Christophe Lopez, Laboratoire de Neurosciences Intégratives et Adaptatives - UMR 7260, Centre Saint Charles, Fédération de Recherche 3C - Case B, Centre National de la Recherche Scientifique - Aix-Marseille Université, 3 Place Victor Hugo, 13331 Marseille Cedex 03, France
e-mail: christophe.lopez@univ-amu.fr

The consequences of vestibular disorders on balance, oculomotor control, and self-motion perception have been extensively described in humans and animals. More recently, vestibular disorders have been related to cognitive deficits in spatial navigation and memory tasks. Less frequently, abnormal bodily perceptions have been described in patients with vestibular disorders. Altered forms of bodily self-consciousness include distorted body image and body schema, disembodied self-location (out-of-body experience), altered sense of agency, as well as more complex experiences of dissociation and detachment from the self (depersonalization). In this article, I suggest that vestibular disorders create sensory conflict or mismatch in multisensory brain regions, producing perceptual incoherence and abnormal body and self perceptions. This hypothesis is based on recent functional mapping of the human vestibular cortex, showing vestibular projections to the primary and secondary somatosensory cortex and in several multisensory areas found to be crucial for bodily self-consciousness.

Keywords: vestibular system, body schema, body image, touch, caloric vestibular stimulation, bodily consciousness, multisensory integration

INTRODUCTION

The consequences of vestibular disorders are dramatic as they incorporate a wide range of symptoms including vertigo, loss of balance, and blurred vision. It is accepted that vertigo results from the activation of the vestibulo-thalamo-cortical pathways, postural instability and falls from abnormal vestibulo-spinal reflexes, and blurred vision from impaired vestibulo-ocular reflexes (Curthoys and Halmagyi, 1995; Borel et al., 2008). More recently, deficits in spatial navigation and memory tasks have been related to vestibular disorders, presumably due to vestibular projections to the cortex and hippocampus (Smith, 1997; Brandt et al., 2005).

In addition to these deficits, vestibular patients sometimes report abnormal bodily perceptions. The role of vestibular organs in bodily perceptions has captured the attention of pioneering researches on body representations such as those of Bonnier (1893, 1905), Schilder (1935); Lhermitte (1939), and Menninger-Lerchenthal (1946). These authors reported cases of patients losing connections with their body, experiencing deformations of their body, or disembodiment. Yet, the mechanisms underpinning these disorders remain poorly understood. One reason is that bodily disorders have to date not been quantified experimentally in vestibular patients despite the development of psychophysical methods to measure various bodily experiences (Blanke, 2012). Secondly, the comprehension of how vestibular dysfunction modifies bodily consciousness has been hampered by scarce descriptions of the vestibular cortex. In the present article, I argue that recent progresses in functional mapping of the human vestibular cortex and advances in the neuroscience of bodily self-consciousness afford a neuroscientific explanation of the mechanisms at the basis of bodily disorders in vestibular patients.

A NEUROSCIENTIFIC FRAMEWORK BASED ON THE MULTISENSORY NATURE OF THE VESTIBULO-THALAMO-CORTICAL PATHWAYS

The neuroscientific framework to understand bodily disorders in vestibular patients is based on the multisensory nature of the vestibulo-thalamo-cortical pathways, a finding that was unknown from Bonnier and Schilder when they described the consequences of vertigo on body perception. A vestibulo-visuo-somatosensory convergence has been found in all vestibular relays, including vestibular nuclei, thalamus, and cerebral cortex (see **Figure 1** and **Table 1** for details).

Normal sensorimotor development calibrates synergies between actions and their sensory consequences at both behavioral and neural levels (Held and Hein, 1963). For example, head rotations to the right are normally encoded with leftward optic flow and matching proprioceptive signals from the neck. Corresponding synergistic responses exist in all vestibulo-thalamo-cortical structures and recent studies showed that vestibular and visual responses combine "in a statistically optimal fashion," in accordance with the predictions of Bayesian models (MacNeilage et al., 2007; Fetsch et al., 2012). Importantly, sensory conflicts may disorganize calibrated synergies at the neural level (e.g., visuo-vestibular mismatch alters neural responses in vestibular nuclei; Waespe and Henn, 1978). Here, I propose similar mismatch is produced by various peripheral vestibular disorders (e.g., Menière's disease, vestibular neuritis). I suggest that vestibular disorders provide the brain with erroneous vestibular signals about current self-motion and position, and create *sensory conflicts* (or *mismatch*) leading to a *perceptual incoherence*. That is, abnormal vestibular signals would induce misinterpretation of tactile, proprioceptive

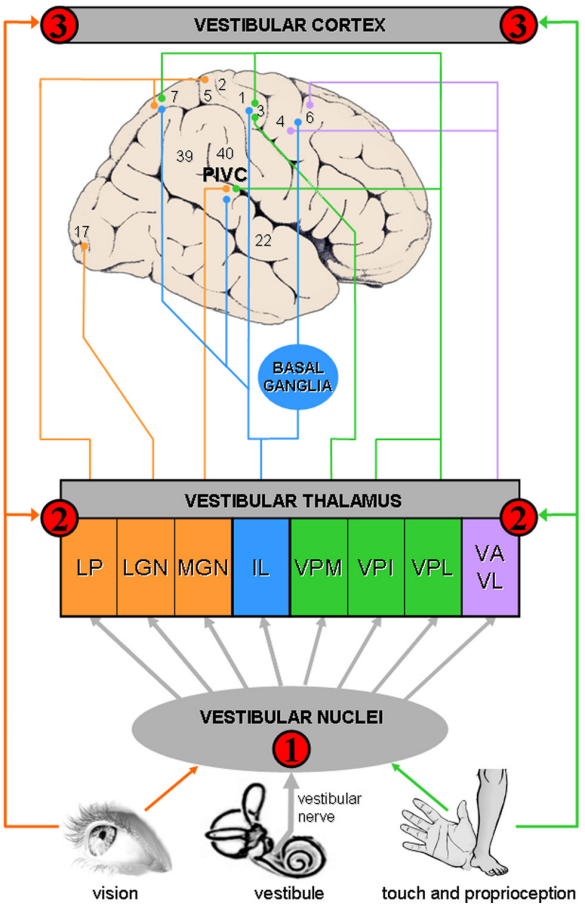


FIGURE 1 | Convergence of vestibular, visual, and somatosensory signals in vestibulo-thalamo-cortical structures. The schema summarizes animal and human data, showing multisensory convergence in three vestibular relays (see also **Table 1** for details): ❶ Vestibular signals are first processed in the *vestibular nuclei* in the brainstem, a region that is highly multisensory. ❷ A second level of vestibular processing takes place in the *thalamus*. Multiple thalamic nuclei contain neurons that respond to vestibular stimulation such as the ventroposterior complex (VPM, ventral posterior medial nucleus; VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus), ventroanterior (VA) and ventrolateral (VL) nuclear complex, intralaminar nuclei (IL), thalamic posterior nuclear group (MGN, medial geniculate nucleus; LGN, lateral geniculate nucleus) and lateral posterior nucleus (LP). Most of these thalamic nuclei contain multisensory neurons. ❸ A third level of vestibular processing occurs in the *cerebral cortex*. Neuroimaging studies used caloric (CVS) and galvanic (GVS) vestibular stimulation and revealed activations centered on the insula, parietal operculum, and temporo-parietal junction (Lopez et al., 2012a; zu Eulenburg et al., 2012). This area may be similar to a region known as the *parieto-insular vestibular cortex* (PIVC) in monkeys (Grüsser et al., 1990a,b; Guldin and Grüsser, 1998; Chen et al., 2010). The PIVC is considered the core region of the vestibular cortex because it is strongly connected or interconnected with most of the other vestibular cortical areas. At least 10 other cortical areas process vestibular signals including somatosensory (areas 2 and 3), superior parietal, cingulate, and premotor cortex.

and visual signals from the body and, as a consequence, distort bodily self-experience. In support of this view are recent data on self-motion perception showing that even in the case of large visual–vestibular conflicts, vestibular information is not disregarded and both signals are "mandatorily fused" (Prsa et al., 2012). Other studies suggest that during multisensory conflicts, vestibular cues are weighted higher (Butler et al., 2010; Fetsch et al., 2012). These data indicate that participants strongly rely on vestibular signals, even when this information contradicts other sensory cues.

In the following sections, I describe a detailed neuroscientific account of how vestibular dysfunction can distort various aspects of the bodily self.

DISTORTED BODY SCHEMA AND BODY IMAGE

CLINICAL DESCRIPTION

Vestibular disorders may impair two fundamental aspects of mental body representations known as *body schema* and *body image*. They refer to different types of representations of body configuration and metric properties, including the size and shape of body parts, and body position in space (e.g., Gallagher, 2005; Berlucchi and Aglioti, 2010; de Vignemont, 2010; Longo et al., 2010; Serino and Haggard, 2010). Although body schema and body image have been proposed to be of mostly proprioceptive and visual origin, a vestibular contribution was postulated over a century ago. Bonnier (1893, 1905) described striking examples of distorted perceptions of the body shape and size in vestibular patients. For example, one of his patients "felt his head became enormous, immense, losing itself in the air; his body disappeared and his whole being was reduced to only his face." Interestingly, Bonnier coined the term "*aschématie*" (indicating a "loss" of the *schema*) to describe distorted representations of the volume, shape, and position of the body and body segments (Vallar and Papagno, 2003; Vallar and Rode, 2009). Several decades later, Schilder (1935) described distorted body schema and image in vestibular patients who reported that the "neck swells during dizziness," "extremities had become larger," or "feet seem to elongate" (p. 117). Altogether, these sensations are comparable to neurological symptoms of *asomatognosia* (e.g., Dieguez et al., 2007), even if evoked solely by peripheral vestibular disorders.

EXPERIMENTAL EVIDENCE

Several lines of evidence from neurology and experimental psychology support the idea that abnormal body image and schema might change due to misinterpretation of bodily signals created by vestibular disorders. All of them are based on studies showing the influence of caloric (CVS) and galvanic (GVS) vestibular stimulation on the perceived shape and size of the body. Rode et al. (2012) described a patient with Wallenberg's syndrome who reported a macrosomatognosia restricted to his left hemiface. In this patient, CVS temporarily alleviated distorted face perception. CVS also changed the perceived shape and position of phantom limbs in paraplegics (Le Chapelain et al., 2001). Similarly, CVS evoked the perception of a phantom limb in amputees who did not experience phantoms before, or altered the phantom perception in those who experienced phantoms already (André et al., 2001). This indicates that CVS can influence mental representations of a no-longer existing body segment and suggests that vestibular signals project to multisensory brain regions representing the body's metric properties. Yet, these observations were based

Table 1 | Evidence of multisensory integration in three vestibulo-thalamo-cortical structures.

Anatomical structure	Evidence of multisensory integration
Vestibular nuclei	Vestibular nuclei neurons respond to vestibular, visual (optokinetic stimulation: Waespe and Henn, 1978), tactile, proprioceptive (Roy and Cullen, 2004) and eye movements signals (Tomlinson and Robinson, 1984). These neurons integrate signals from otoliths and semicircular canals afferents to discriminate between head translations and head tilts, as well as to distinguish between active (or voluntary) and passive (or involuntary) head movements (review in Angelaki and Cullen, 2008).
Thalamus	Vestibular thalamic neurons are characterized by very similar responses that have been described for vestibular nuclei neurons, i.e., they respond to visual, tactile, and proprioceptive stimuli (review in Lopez and Blanke, 2011). For example, about half of the vestibular neurons in the cat LGN respond to optokinetic stimulation (Magnin and Putkonen, 1978) and most of them are also driven by saccadic eye movements. Vestibular neurons in the VPL, VPM, and VPI respond to proprioceptive signals from joints and muscles (Deecke et al., 1977; Blum and Gilman, 1979) and code for passive movements of the neck, shoulders, legs, and vertebral column. Thalamic vestibular neurons also respond to tactile stimulation applied to the animal's paws (Sans et al., 1970).
Cerebral cortex	Vestibulo-visuo-somatosensory convergence has been reported in the PIVC, at the junction of the insula with the retroinsular and somatosensory cortex (Grüsser et al., 1990a,b; Guldin and Grüsser, 1998). Visual–vestibular convergence has also been reported in the extrastriate visual area MST, a major region for self-motion perception based on optic flows (Bremmer et al., 1999; Gu et al., 2006). Vestibular–somatosensory convergence has been reported in the intraparietal sulcus and primary somatosensory cortex in monkeys (areas 2v and 3av in the hand/arm and neck/trunk representations) and in the secondary somatosensory cortex in humans (Schwarz and Fredrickson, 1971; Bottini et al., 1995, 2001, 2005; Guldin and Grüsser, 1998; Bremmer et al., 2002; Fasold et al., 2008).

only on patients' reports. Lopez et al. (2012b) demonstrated similar influence of CVS by using psychophysical measures in healthy participants. The influence of CVS on the perceived shape and size of the body was measured using a tactile distance comparison task and a proprioceptive judgment task. The results showed that CVS known to stimulate the right cerebral hemisphere modified the perceived size of the left hand, that appeared to be enlarged. This finding was later corroborated by the application of GVS (Ferrè et al., 2013).

NEUROPHYSIOLOGICAL HYPOTHESIS

Neuroimaging studies have revealed the implication of the posterior parietal cortex in body shape and size perception. In particular, the perception of the current position of body segments is thought to rely on the superior parietal lobule and intraparietal region (Wolpert et al., 1998; Félician et al., 2004; Corradi-Dell'Acqua et al., 2008, 2009). The inferior parietal lobule is also particularly relevant since electrical stimulation of the angular gyrus distorted body schema in epileptic patients (Blanke et al., 2002) and because transcranial direct current stimulation applied over the right angular gyrus modified body representations (Spitoni et al., 2013). Neuroimaging studies further revealed the implication of the parietal operculum and posterior insula as they contain somatotopic representations of the body (Eickhoff et al., 2007; Corradi-Dell'Acqua et al., 2009; Hashimoto and Iriki, 2013). Importantly, these parietal and insular regions process vestibular signals and the parietal operculum has even been proposed as the core vestibular cortex (Guldin and Grüsser, 1998; Eickhoff et al., 2006; Lopez et al., 2012a; zu Eulenburg et al., 2012). It is interesting to note that animal data revealed vestibulo-somatosensory convergence in parietal cortex, intraparietal sulcus, and operculo-insular cortex (Grüsser et al., 1990a,b, 1994; Bremmer et al., 2002). Bottini and colleagues showed that the parieto-insular cortex is a region where CVS interferes with tactile perception (Bottini et al., 1995, 2001, 2005; Ferrè et al., 2012). Accordingly, abnormal vestibular signals arriving in these regions during vertigo attacks may interfere with somatosensory processing. The misinterpretation of postural somesthetic signals from the neck may explain the patients' reports that their neck or head is enlarged. In support of this view is the fact that CVS and GVS produce similar effects in healthy volunteers (Lopez et al., 2012b; Ferrè et al., 2013).

EMBODIMENT OR THE SENSE OF UNITY BETWEEN THE SELF AND THE BODY

CLINICAL DESCRIPTION

Vestibular patients may lose connection with their body and may be subject to an out-of-body experience (OBE). During an OBE, subjects localize their self outside their body, at a location that is often elevated (i.e., floating in the room), and experience seeing the environment from this disembodied location. Subjects may also experience seeing their own body (i.e., autoscopy), a double with which they strongly self-identify (Brugger, 1997; Blanke et al., 2004; Blanke and Mohr, 2005; Lopez et al., 2008; Blanke, 2012). Yet, clear cases of full-blown OBEs due to vestibular disorders seem very rare. Bonnier (1905) described the case of a loss of self–body unity: "it seemed to [the patient] that he was divided into two persons, one who had not changed posture, and another new person on his right, looking somewhat outwardly. Then the two somatic individuals approached each other, merged, and the vertigo disappeared." Illusory perceptions of doubles in vestibular pathology were also reported by Skworzoff (1931): one patient

saw herself (i.e. autoscopy) for a moment in day light (Case 5, p. 764). Another patient saw and felt every day his own double (Case 6, p. 764). The same patient also reported in some instances sensations of flying, which could be evocative of an otolithic dysfunction.

EXPERIMENTAL EVIDENCE

Vestibular stimulation in healthy participants can strongly modify experienced self-location. GVS creates illusory motion of the entire body, i.e., dissociation between the perceived self-location (that appears tilted toward the cathode) and physical body location (Fitzpatrick and Day, 2004; Lenggenhager et al., 2008). Lopez et al. (2008) have proposed that such dissociation between self and body location reflects a type of *partial disembodiment* that is reminiscent of OBEs of neurological origin. Another indirect evidence of a vestibular contribution to embodied self-location comes from the observation that OBEs are more frequent in patients lying than sitting or standing upright (Blanke and Mohr, 2005). According to Green (1968), about 73% of OBEs occur spontaneously when healthy subjects are lying down, and less often in sitting or standing subjects, suggesting a strong contribution of gravitational vestibular signals to self-location and embodiment.

NEUROPHYSIOLOGICAL HYPOTHESIS

A neurophysiological model by Blanke and colleagues posits that during OBEs a *triple sensory misintegration*, with conflicting vestibular, visual, and somatosensory signals, may occur in multisensory brain regions such as the temporo-parietal junction (Blanke et al., 2002, 2004; Blanke and Mohr, 2005; Lopez et al., 2008; Blanke, 2012). This model is supported by the fact that vestibular sensations (e.g., floating, lightness, elevation) occur often during OBEs of neurological origin (Devinsky et al., 1989; Blanke et al., 2002, 2004; Lopez et al., 2010; Heydrich et al., 2011). In addition, brain areas that are the most commonly damaged in OBE patients overlap with the vestibular cortex at the temporo-parietal junction (Blanke et al., 2004; Ionta et al., 2011). Altogether, these data suggest a close relation between the phenomenal experience of a disembodied self and vestibular misintegration (Lopez and Blanke, 2007; Lopez et al., 2008; Blanke, 2012). Accordingly, the loss of self–body unity in vestibular patients may be due to sensory mismatch created by vertigo attacks at the temporo-parietal junction and posterior insula, two regions the metabolism of which is strongly disorganized by vestibular disorders (Bense et al., 2004; Alessandrini et al., 2013). Interfering with the temporo-parietal junction by electrical stimulation has also been showed to induce both OBE and vestibular sensations (Penfield, 1955; Blanke et al., 2002; De Ridder et al., 2007). Vertigo attacks may produce a similar type of interference as those intracranial stimulations, but to a weaker extent, since full-blown OBEs were rarely reported in vestibular pathology.

AGENCY

CLINICAL DESCRIPTION

The loss of self–body connection described above is also evident in the motor control domain. A minimal sense of selfhood has been related to the *sense of agency*, the experience of being the agent of one's own actions (Franck et al., 2001; Jeannerod, 2006, 2009). Interestingly, vestibular patients report more often than healthy participants the experience of "not being in control of their self" (Sang et al., 2006; Jauregui-Renaud et al., 2008b). For example, a patient with a bilateral Menière's disease reported during vertigo attacks "watching something happen and not being a part of it. It's just a feeling of not being there, participating in what's going on" (Case 2, p. 532 in Grigsby and Johnston, 1989). Vestibular patients often report that their actions do not seem to match their intentions. Even when tested at a compensated stage of a vestibular loss, patients perceive instability and dizziness during walking and standing despite no evident sign of postural unbalance.

EXPERIMENTAL EVIDENCE

To date, the role of vestibular signals in the sense of agency has not been measured experimentally. However, it has been showed that CVS evoked in healthy participants significantly stronger feeling of "not being in control of the self" than control stimulation (Lopez et al., 2012b). In addition, GVS altered the ability to perform and predict hand movements (Bresciani et al., 2002; Guillaud et al., 2011), but agency was not measured directly in these experiments.

NEUROPHYSIOLOGICAL HYPOTHESIS

Vestibular patients may report altered sense of agency because vestibular organs do not correctly encode the consequences of their actions. Patients tend to underestimate their body displacements and misinterpret the direction of body movements (Cohen, 2000; Borel et al., 2004), revealing the crucial role of vestibular signals in spatial updating during active and passive whole-body motions (e.g., Frissen et al., 2011; Campos et al., 2012). Errors in sensory coding can introduce a mismatch between vestibular, visual, and somatosensory feedback about self-initiated movements, as well as a discrepancy with the efferent signals from the motor command. Behavioral studies showed that agency is based on congruent sensory feedback from one's actions: introducing a mismatch (amplitude or direction of motion) between the visual and proprioceptive consequences of an action impairs agency (Fourneret and Jeannerod, 1998; Farrer et al., 2003b, 2008a; Kannape et al., 2010). I speculate that an additional factor may be responsible for distorted sense of agency in vestibular patients: a *temporal mismatch* between an action and the sensory feedback from this action. Interestingly, perception of time is altered in vestibular patients (Israel et al., 2004) and introducing a delay between the executed and seen movement disturb agency (Franck et al., 2001). Neuroimaging studies have revealed that the insula and the temporo-parietal junction are involved in agency (Spence et al., 1997; Farrer and Frith, 2002; Farrer et al., 2003a, 2004, 2008b). This reiterates the contribution of two main vestibular regions to a crucial bodily experience of self-consciousness. In light of these points, vestibular dysfunctions are therefore likely to create a spatiotemporal mismatch between efferent motor commands and feedback from an action, resulting in a disturbed sense of agency.

DEPERSONALIZATION AND DEREALIZATION

CLINICAL DESCRIPTION

Most of the bodily disturbances described in the previous sections are part of depersonalization, a dissociative disorder characterized

by the loss of familiarity of the self and surrounding and by a detachment from the self, that may be experienced as unreal (Simeon and Abugel, 2006). Early in the last century, Schilder (1914, 1935) already proposed a vestibular contribution to depersonalization and derealization (DD). More recently, Grigsby and Johnston (1989) collected experiences of DD in Menière's disease patients: a patient described DD as "a sense of unreality" and claimed "I feel like I'm outside of myself. I feel like I'm not in myself" (p. 531). Another patient reported "I am not actually being there or having anything to do with my body" (p. 532). More recently, the use of the Cox and Swinson (2002) questionnaire revealed that vestibular patients have more frequent and more severe DD symptoms than controls (Sang et al., 2006; Jauregui-Renaud et al., 2008b). Symptoms included sensations of "déjà vu," "body feels strange" and the experience of feeling "spacey" or "spaced out."

EXPERIMENTAL EVIDENCE

Yen Pik Sang et al. (2006) applied CVS in healthy volunteers and showed that it increased the frequency of DD symptoms such as "surroundings seem strange and unreal," "time seems to pass very slowly" and "body feels strange/different in some way." This finding was confirmed during bilateral CVS (Lopez et al., 2012b). It is not known, however, how long these effects persist.

NEUROPHYSIOLOGICAL HYPOTHESIS

Discrepancy between vestibular and other body-related signals may deteriorate the experience of the body and surroundings, leading to DD. In line with this view is the observation that various sensory dysfunctions increase the frequency of DD symptoms (vestibular, visual, auditory: Jauregui-Renaud et al., 2008a,b; somatosensory: Lenggenhager et al., 2012). The superior temporal and inferior parietal cortices are the best candidates to explain the vestibular influence on DD. During stimulation of the superior temporal cortex, Penfield (1947, 1955) evoked sensations of "déjà vu" and altered self-body relations ("I feel queer, as though I were floating away" and "I have a queer sensation as if I am not here," Penfield, 1947, p. 342). Interestingly, the sites of these stimulations overlapped those where vestibular sensations were evoked. In a PET study, Simeon et al. (2000) showed that DD were related to changes in brain metabolisms in regions that were also activated by CVS and GVS (superior temporal gyrus and temporo-parietal junction). Of particular interest here is the study by Bense et al. (2004) showing that very similar regions have altered metabolism during vestibular neuritis. This anatomical overlap strongly suggests that vestibular dysfunction disorganizes brain metabolism, multisensory integration, and eventually structure and connections in the multisensory temporo-parietal cortex, and this may be the underlying mechanism of DD in vestibular patients.

CONCLUSION

A better understanding of cortical vestibular processing, as well as of how CVS and GVS influence body and self perceptions, has provided the basis for a neuroscientific account of a so far under-recognized type of vestibular symptom – alterations in bodily self-consciousness. I have summarized evidence showing that abnormal forms of bodily self-consciousness in vestibular disorders may result from sensory conflict or mismatch in multisensory brain regions. This hypothesis should now be put under scientific scrutiny by correlating changes in bodily self-consciousness (e.g., subjective reports using DD questionnaires and objective measures of altered sense of agency and self-location; Kannape et al., 2010) with changes in metabolism and structure in the vestibular cortex (e.g., Bense et al., 2004; voxel-based morphometry: zu Eulenburg et al., 2010). In addition, I have drawn parallels between experimental evidence and clinical observations in vestibular patients to clarify the neural and sensory mechanisms of bodily self-consciousness. Future research in the field should endeavor to make the same comparisons to further our understanding of the underlying multisensory mechanisms of bodily self-consciousness (see Blanke, 2012). In particular, several bodily experiences should now be systematically quantified in vestibular patients to obtain a full description of the consequences of vestibular dysfunctions, including changes in the patient's *self*, mood, and personality. I am optimistic that these data will also impact on the multisensory models of self-consciousness currently developed by neuroscientists and philosophers and in which the contribution of the vestibular system is often neglected.

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Spatial cognition, body representation and affective processes: the role of vestibular information beyond ocular reflexes and control of posture

Fred W. Mast[1,2]*, Nora Preuss[1,2], Matthias Hartmann[1,2] and Luzia Grabherr[3]

[1] *Department of Psychology, University of Bern, Bern, Switzerland*
[2] *Center for Cognition, Learning and Memory, University of Bern, Bern, Switzerland*
[3] *Sansom Institute for Health Research, University of South Australia, Adelaide, SA, Australia*

Edited by:
Stephane Besnard, INSERM U1075, France

Reviewed by:
Caroline Gurvich, Monash University, Australia
Kathrine Jauregui-Renaud, Instituto Mexicano del Seguro Social, Mexico
Lionel Bringoux, Aix-Marseille Université—Institut des Sciences du Mouvement E.J. Marey UMR CNRS 7287, France

***Correspondence:**
Fred W. Mast, Department of Psychology, University of Bern, Fabrikstrasse 8, 3012 Bern, Switzerland
e-mail: fred.mast@psy.unibe.ch

A growing number of studies in humans demonstrate the involvement of vestibular information in tasks that are seemingly remote from well-known functions such as space constancy or postural control. In this review article we point out three emerging streams of research highlighting the importance of vestibular input: (1) *Spatial Cognition*: Modulation of vestibular signals can induce specific changes in spatial cognitive tasks like mental imagery and the processing of numbers. This has been shown in studies manipulating body orientation (changing the input from the otoliths), body rotation (changing the input from the semicircular canals), in clinical findings with vestibular patients, and in studies carried out in microgravity. There is also an effect in the reverse direction; top-down processes can affect perception of vestibular stimuli. (2) *Body Representation*: Numerous studies demonstrate that vestibular stimulation changes the representation of body parts, and sensitivity to tactile input or pain. Thus, the vestibular system plays an integral role in multisensory coordination of body representation. (3) *Affective Processes and Disorders*: Studies in psychiatric patients and patients with a vestibular disorder report a high comorbidity of vestibular dysfunctions and psychiatric symptoms. Recent studies investigated the beneficial effect of vestibular stimulation on psychiatric disorders, and how vestibular input can change mood and affect. These three emerging streams of research in vestibular science are—at least in part—associated with different neuronal core mechanisms. Spatial transformations draw on parietal areas, body representation is associated with somatosensory areas, and affective processes involve insular and cingulate cortices, all of which receive vestibular input. Even though a wide range of different vestibular cortical projection areas has been ascertained, their functionality still is scarcely understood.

Keywords: vestibular system, vestibular imagery, multisensory integration, mental rotation, body representation, body schema, affect, mood

INTRODUCTION

The wide majority of vestibular research concerns basic oculomotor mechanisms and postural control. Over several decades a substantial body of research has been ascertained, including the perception of self-motion and neuronal circuits that underlie the vestibulo-ocular reflex (VOR). The nature of the VOR has inspired computational models with precisely defined input parameters, and single-cell recordings have provided first insights into the brain areas that are involved in the processing of vestibular input (Grüsser et al., 1990). With the advent of neuroimaging, researchers started to use ways to induce vestibular sensations while brain activation was assessed. This is a challenging procedure because most current neuroimaging techniques require a stable head position, and it is therefore not possible to investigate the neuronal correlates of vestibular stimuli as they occur during natural head movements. However, the use of caloric vestibular stimulation (CVS), galvanic vestibular stimulation (GVS), and high-frequency auditory stimuli (clicks or tone bursts) allow for inducing vestibular stimulation while the head remains stationary. This research provided important findings about the human cortical areas associated with the processing of vestibular stimulation. The exact locations and functions of vestibular cortical areas are still a matter of debate (Lopez and Blanke, 2011). A recent meta-analysis by Lopez et al. (2012b) could identify the core regions of the human vestibular cortex. These areas involve the Sylvian fissure, insula, retroinsular cortex, fronto-parietal operculum, and cingulate cortex. Despite some discrepancies between different studies about the cortical areas involved in vestibular stimulation (Lopez et al., 2012b; zu Eulenburg et al., 2012) there is absolutely

no doubt about the existence of widespread cortical vestibular representations.

Interestingly, there is still a lack of knowledge about the functions these cortical vestibular networks are involved in and with what other networks they overlap. For example, it has been shown that neurons in the gaze-related frontal eye fields are modulated by rotation and translation (Ebata et al., 2004). In middle superior temporal area (MSTd), neurons respond to inertial motion in darkness. These neurons represent visual-vestibular integration for heading perception (Gu et al., 2007). Neurons in the ventral intraparietal area (VIP) respond to passive translations (Schlack et al., 2002) and rotations (Bremmer et al., 2002). These areas in addition to the parieto-insular vestibular cortex (PIVC) demonstrate the cortical involvement in the processing of self-motion perception, heading and gaze control.

Most vestibular research focuses on the encoding of gravito-inertial signals and this is evident given the profound knowledge about the vestibular end organ, and its projections to brain stem and cerebellar areas. However, we think it will add to a more complete understanding of vestibular functions when including higher processing areas in future research. The use of neuroimaging will certainly contribute but it is noteworthy to point out these techniques are in essence correlational and do not permit drawing causal conclusions about the functions that are associated with a particular pattern of brain activation. In our view, the advancement of the field depends largely on the future use of innovative behavioral techniques, the use of which is absolutely necessary to tap into the mechanisms that underlie vestibular cortical processes.

PubMed and Web of Science were the main databases that we used in order to search the literature. The key word "vestibular" was used in combination with the search terms "cognition", "mental rotation" "spatial", "body representation", "somatosensory", "tactile", "body schema" and "pain" to retrieve the relevant articles. The identified literature was then hand-searched, and we excluded articles focusing exclusively on physiological mechanisms, remotely related neurological disorders (e.g., Morbus Parkinson), animal research, and, for the most part, memory research. The latter has been addressed in several review papers already, and therefore became a field of research that receives considerable attention already (Smith et al., 2010; Smith and Zheng, 2013). The main focus of this review article lies on studies using a manipulation of the vestibular input (e.g., body motion, CVS, GVS). Furthermore, the references of the included articles were screened and new studies that cite the identified articles were taken into consideration. The remaining articles can be clustered in three research areas: *spatial cognition*, *body representation*, and *affective processes and disorders*. We will outline below the relevant state of research in each of these areas separately. In each section, we discuss in brief the most relevant issues tied to the respective research area, followed by a broader discussion of higher vestibular processing at the end of this article.

SPATIAL COGNITION

The vestibular system has been identified as one of the most important sources of our sense of spatial orientation (see handbook chapter by Merfeld, 2012). The contribution of vestibular signals for various space-related cognitive functions becomes evident in patients suffering from vestibular loss. These patients show impairments in path integration, navigation and spatial memory (e.g., Brandt et al., 2005; Péruch et al., 2005; Guidetti et al., 2008). For example, patients with bilateral vestibular loss showed impaired performance in a virtual version of the Morris water maze (Schautzer et al., 2003; Brandt et al., 2005). Interestingly, these patients also showed decreased hippocampal volume (Brandt et al., 2005). In patients with unilateral vestibular loss, spatial memory deficits are subtle and they are not accompanied by a hippocampal atrophy (Hüfner et al., 2007, 2009). A substantial amount of research on the vestibular involvement in spatial memory has been gained from studies with vestibular-lesioned rodents. This research strongly supports the notion that vestibular input is required for navigation and spatial memory (e.g., Baek et al., 2010; Besnard et al., 2012; Zheng et al., 2012). While no effects on hippocampal volume were found (Zheng et al., 2012), vestibular lesions can disrupt hippocampal theta rhythm (Russell et al., 2006), eliminate directional sensitivity in hippocampal head direction cells (Stackman et al., 2002), and lead to neurochemical and neurophysiological changes (Zheng et al., 2001, 2013). See Smith et al. (2010) for a complete review on the implications of vestibular information in memory in humans and animals alike. In this context it is noteworthy that in healthy human subjects, vestibular stimulation was found to enhance spatial and non-spatial memory (Bächtold et al., 2001; Wilkinson et al., 2008).

Interestingly, the vestibular system is not only involved in the processing of motion in the physical world, it also seems to play an important role in building and maintaining a mental representation of the world. Even though we are bound to physical space, we are able to represent objects and movements mentally in order to optimally predict actions, react to events, and solve problems. A case in point is mental rotation. Shepard and Metzler (1971) have shown that people rotate a mental representation of an object in order to match it with another similar object. The response times increase with increasing angular disparity between two objects, and thus embody the characteristics of real rotations. It has been shown that the mechanisms that underlie mental rotation processes are not exclusively visual in nature but they also involve motor processes (e.g., Wraga et al., 2005, for a review see Kosslyn et al., 2001). Not only can we rotate in our mind visual representations of objects but also a representation of our own body or body parts. This is the case when one imagines what one would see from a different viewpoint. Viewer rotations operate on the representation of one's own body and they can be performed independently of the actual state of the physical body. Vestibular areas process body information caused by real body movements (translations and rotations), and, given the large amount of cortical vestibular representations, it is conceivable that some of the areas are drawn upon in an off-line mode. This would imply that brain areas dedicated to the processing of real body motion are also in the service of mental imagery when whole-body motion is merely imagined but not executed. Interestingly, there is so far only one neuroimaging study testing vestibular imagery (zu Eulenburg et al., 2013a). They found activation in

the inferior parietal lobules, and these activations were stronger in the left hemisphere. A left sided parietal activation is in line with several studies on imagined self-rotations (e.g., Just et al., 2001; Vingerhoets et al., 2001) even though the activation pattern reported by zu Eulenburg et al. (2013a) was more inferior in the parietal lobe. Zu Eulenburg et al. first exposed participants to yaw rotation in an upright position, and the participants later had to recall this sensation while lying supine in the scanner. Participants were not debriefed about the strategy they applied when they recalled previous vestibular sensations. Had the participants in the supine position reproduced in egocentric coordinates the yaw stimulation they experienced on the chair, it would have resulted in an imagined barbecue rotation, which implies a change in body position with respect to gravity. Changes in body position with respect to gravity can influence performance in mental imagery tasks (Mast et al., 2003). Clearly, behavioral techniques need to be refined in order to better assess what participants are doing when they recall from memory previously experienced vestibular sensations. As pointed out by zu Eulenburg et al. (2013a), they used a non-visual first-person strategy that differed from similar mental body transformation tasks, which require visual stimuli. Interestingly, no activation in many other areas belonging to the vestibular network (e.g., the human analog of the PIVC) has been revealed. Another neuroimaging study investigated imagined locomotion and the results show an overlap with real locomotion (la Fougère et al., 2010). However, imagined locomotion was associated with early visual activation and this suggests that participants used a visual rather than vestibular strategy. It is likely that participants imagined self-motion by means of visual flow, and, indeed, there was a deactivation of vestibular areas such as the inferior parietal lobule during imagery. Vestibular deactivation has been reported repeatedly during visually induced self-motion (e.g., Brandt et al., 2002). This discrepancy illustrates that subtle changes in how people perform mental imagery tasks can substantially change brain activation, and it will be a challenge for future research to narrow down the cognitive processes. For example, it needs to be controlled whether participants imagine as vividly as possible the experience of self-motion with or without the aid of imagined visual stimuli. A similar distinction is known for the assessment of motor imagery, for which a kinesthetic[1] subscale and a visual subscale have been defined in the Vividness of Motor Imagery Questionnaire (VMIQ; Isaac et al., 1986). Inevitably, locomotion in real life stimulates the vestibular system, and if imagined locomotion reenacts the characteristics of real body motion we would expect involvement of vestibular areas so that kinesthetic imagery has more vivid perceptual qualities. However, it is possible that vestibular imagery may be inherently different from other types of sensory imagery such as visual or auditory. Therefore, it may be difficult for participants to perform vestibular imagery without relying on other sensory input (e.g., tactile or visual), which often accompanies the actual physical motion. However, vestibular stimulation can provoke a conscious experience of its own, and we are able to perceive self-motion despite the absence of concurrent extra-vestibular stimulation.

[1]The VMIQ-2 is a revised version of the original VMIQ (Roberts et al., 2008). It makes a more precise distinction between internal imagery (participants visually imagine performing an action) and kinesthetic imagery (participants imagine themselves performing an action).

VESTIBULAR INFLUENCES ON SPATIAL COGNITION

An example of how vestibular input can interact with spatial processing can be found in the well established subjective visual vertical task (SVV). A luminous line is set to the apparently vertical orientation, and it has been shown that the SVV depends on the body orientation of the observer (e.g., Tarnutzer et al., 2010). Interestingly, variation of task demands changes the contribution of the gravity-receptive signals (Bronstein, 1999). Clinical studies with vestibular patients suggest less impairment in the perception of body position (Bisdorff et al., 1996; Bringoux et al., 2002) or the adjustment of the gravity-referenced eye level (Bringoux et al., 2007) when compared to the typical pattern known from the assessment of the SVV. Spatial orientation tasks are an interesting front door for further exploring spatial cognition because performance in cognitive tasks also changes as a function of body position. For example, changing the inputs of the otoliths by means of the orientation of the observer has an impact on how objects are mentally manipulated (Corballis et al., 1976, 1978; Gaunet and Berthoz, 2000; Mast et al., 2003). In the same vein, specific changes in mental transformation tasks have been investigated through own-body rotation (van Elk and Blanke, 2013), changing the input from the semicircular canals by CVS (Mast et al., 2006; Falconer and Mast, 2012), changing the input of the vestibular nerve by GVS (Lenggenhager et al., 2008; Dilda et al., 2012), microgravity studies (Matsakis et al., 1993; Leone et al., 1995; Grabherr et al., 2007; Dalecki et al., 2013) and clinical studies with vestibular patients (Grabherr et al., 2011; Péruch et al., 2011; Candidi et al., 2013). It is important to point out that some studies provide evidence that vestibular input influences performance in mental rotation tasks only then when the task involves a representation of one's own body or perspective (Lenggenhager et al., 2008; Dilda et al., 2012; Falconer and Mast, 2012). Congruent motion can facilitate mental rotation of one's own body (Falconer and Mast, 2012; van Elk and Blanke, 2013) while absent or disturbed vestibular input can impair it (Grabherr et al., 2007; Lenggenhager et al., 2008). Some studies on vestibular patients show deficits in mental transformation of bodies and objects alike, suggesting that spatial-cognitive abilities are more globally impaired in these patients (Péruch et al., 2011; Candidi et al., 2013), whereas there is also evidence for a more pronounced impairment in mental rotation of bodies (Grabherr et al., 2011). These studies demonstrate that vestibular input or the lack thereof can interfere with or facilitate specific cognitive tasks. Even though the sum of these studies do not yet provide a fully coherent picture as to how vestibular processes are nested within spatial transformation abilities, they provide first evidence that the processing of vestibular information overlaps with specific cognitive spatial abilities. It will be interesting to investigate how the effects of body position on cognitive tasks relate to the spatial orientation tasks mentioned above, and whether the underlying gravity-receptive mechanisms differ between tasks.

The vestibular-cognitive interactions described above focused on cognitive processes that included mental spatial transformation of an object, body or body part. Beside this, vestibular

input can also influence the processing of information that is represented in a specific spatial order. An illustrative example are numbers. In Western cultures, small numbers are cognitively represented in the left, and large numbers in the right side of space, following the concept of the "mental number line" (see Hubbard et al., 2005, for a review). The small-left and large-right-association also depends on vestibular information. For example, tuning the head to the left side leads to the production of smaller numbers than turning the head to the right side in a random number generation task (Loetscher et al., 2008). Similar effects have been found with horizontal passive whole-body motion in the dark, thus separating the vestibular input from neck afferences (Hartmann et al., 2012b; see also Hartmann et al., 2012a). A related concept of the mental number line is the mental time line, assuming that also temporal events are represented with a spatial entity. According to the concept of the mental time line, past events are associated with left or back space, and future events with right or front space (e.g., Arzy et al., 2009; Ulrich and Maienborn, 2010; Ulrich et al., 2012). In accordance with this, Miles et al. (2010) found that thinking about the past is accompanied by backward body sway, and thinking about the future by forward body sway. Similarly, it has been shown that future-related words were processed faster during forward when compared to backward passive whole-body motion, pointing again to vestibular contributions to these effects (Hartmann and Mast, 2012). A possible explanation for these findings could be the shift in spatial attention that is associated with the displacement of the body in space. Passive self-motion around the earth-vertical axis has been shown to shift spatial attention in the direction of motion: leftward motion facilitated the processing of a dot presented on the left side of the screen or a tactile stimulus applied on the left side of the body, whereas the opposite pattern was found for rightward motion (Figliozzi et al., 2005). Such a shift in spatial attention could also influence the processing of spatially represented stimuli. For example, moving leftwards makes small numbers more accessible because spatial attention is shifted to the left side of the mental number line.

COGNITIVE INFLUENCE ON VESTIBULAR PERCEPTION

Interestingly, there is also an effect in the reverse direction: cognitive processes can change the perception of vestibular stimuli. To date, it is still widely believed that self-motion perception is determined by characteristics of sensory receptors, and it has been shown that vection induces subtle sensorimotor changes in arm movement control (Bringoux et al., 2012). Interestingly, self-motion perception can be modulated by high-level visual input like seeing another person in motion (Lopez et al., 2013, see Deroualle and Lopez, 2014, this issue, for a review on vestibular information in social cognition). More surprisingly, Wertheim et al. (2001) showed that prior knowledge of motion can influence the perception of passive self-motion. Recently, Hartmann et al. (2012b) could demonstrate that processing small or larger numbers facilitated the detection of leftward or rightward rotation. Yet other studies have used mental imagery of visual motion, which also influences the perception of vestibular stimuli (Mast et al., 1999, 2001; Mertz and Lepecq, 2001). For example, mental imagery of self-motion by means of imagined vection stimuli can influence the perception of physical self-motion; recognition of target acceleration was improved when participants imagined themselves passively moving in the same direction, and, likewise, performance was impaired when the direction of imagined and perceived self-motion were incongruent (Mertz et al., 2000).

What needs to be more thoroughly investigated in future research is whether changes in thresholds have their origin at the level of sensitivity or at a later decision stage. Hartmann et al. (2013) could show that sensitivity in self-motion perception cannot be changed as a function of perceptual learning, and therefore, it is more likely that a bias rather than sensitivity is responsible for changes in thresholds. It is interesting that Rodionov et al. (2004) have shown that imagined body rotations can induce a typical nystagmus in healthy participants, and this findings suggests that imagined movements can penetrate the level of early oculomotor mechanisms. Gianna-Poulin et al. (2001), however, did not find a reduction of postrotatory nystagmus during imagined body tilts after prolonged yaw rotation. They conclude that velocity storage mechanisms are not malleable by cortical input. More research is needed to better investigate under which conditions and what kind of top-down processes can change oculomotor control. More specific knowledge about top-down influences on vestibular perception and vestibular reflexive responses may likely have a potential for application. For example, the use of cognitive procedures such as mental imagery training may be beneficial in vestibular rehabilitation (Lopez et al., 2011).

BODY REPRESENTATION

The sense we have of our own body, that we own it and have agency over it, that we can integrate our physical selves with our environment in functional ways, are sophisticated capacities that are often taken for granted. Head and Holmes (1911) proposed the terms body schema (related to proprioception and movement) and Schilder (1935) first coined the term body image (related to bodily awareness), and they described what our body feels like, and how we feel about our body. Ever since this terminology has been introduced there was ambiguity and confusion about what these capacities described. The current review relates to both proprioceptive capacity and bodily awareness. We will use the term *body representation* to collectively describe these capacities. Several clinical phenomena consistent with disruption of body representation were attenuated after CVS (for an overview on bodily disorders see de Vignemont, 2010, Table 1). These conditions include tactile extinction (Vallar et al., 1993; Kerkhoff et al., 2011; Schmidt et al., 2013), personal neglect (Cappa et al., 1987; Vallar et al., 1990), hemianesthesia (Vallar et al., 1990; Bottini et al., 2005), anosognosia (Cappa et al., 1987), somatoparaphrenia (Bisiach et al., 1991; Rode et al., 1992), macrosomatognosia (Rode et al., 2012) and phantom limb sensations (André et al., 2001; le Chapelain et al., 2001). Investigations into these phenomena have a long tradition, but only recently a few research groups began investigating potential effects of vestibular stimulation on tactile perception in healthy subjects. First, left cold CVS[2] improved *tactile perception* in both

[2]Known to activate predominantly the right hemisphere (Miller and Ngo, 2007).

hands (Ferrè et al., 2011, 2013a). Similar results were found when using left anodal and right cathodal GVS[3]—tactile perception was bilaterally enhanced—while right anodal and left cathodal GVS[4] as well as sham stimulation had no effects (Ferrè et al., 2013b). Second, *tactile localization* was affected by GVS. Namely, tactile localization on the hand dorsum was shifted in the proximal–distal axis toward the wrist. This localization bias was greater after right anodal and left cathodal GVS compared to left anodal and right cathodal GVS (Ferrè et al., 2013c). Third, Lopez et al. (2012c) used left cold, right warm CVS to investigate the influence of vestibular input on the body schema. Participants performed a tactile distance comparison and stimuli applied to the hand were judged to be longer during CVS when compared to sham stimulation. In a second experiment they showed that the perceived size of the hand increased during CVS with respect to sham stimulation, implying an enlarged *somatorepresentation* due to vestibular stimulation. However, this is in contrast to Ferrè et al. (2013c) who found no effects of GVS on this type of task. Moreover, Lopez et al. (2010) used the "rubber hand illusion" paradigm and they found an increased illusory ownership for the left rubber hand and illusory location of touch when applying left anodal and right cathodal GVS. No effects were found when sham stimulation or right anodal and left cathodal GVS were used. Interestingly, no influences on the "objective" proprioceptive drift were observed (Lopez et al., 2010, 2012a). These studies extend earlier clinical reports about the association of vestibular dysfunction and abnormal bodily sensations that have been identified over a century ago (Bonnier, 2009).

Influences of vestibular stimulation on tactile perception and body representation in healthy subjects and patients alike seem plausible given the anatomical overlap of vestibular and somatosensory networks (Lopez and Blanke, 2011; Lopez et al., 2012b). A recent fMRI study that applied tactile and CVS in the same subjects revealed important overlapping cortical activation in the dorsal posterior insula and the parietal operculum (zu Eulenburg et al., 2013b). Moreover, an EEG study assessing somatosensory-evoked potentials elicited by electrical left median nerve stimulation before and after left cold CVS found a bilaterally enhanced N80 component, presumably generated in the parietal operculum (Ferrè et al., 2012). More research is needed to better control for the specificity of vestibular stimulation, and how long its effects persist over time.

Recently, Ferrè et al. (2013a) and Bottini et al. (2013, this issue) argue that CVS exerts specific effects that can be interpreted as sensory signal management. By modulating other sensory modalities vestibular signals can help to flexibly adjust to changing information with respect to the relation between the body and the external world, and therefore better anticipate future motor and perceptual events. According to the authors, CVS activates specific cortico-subcortical networks linking vestibular and somatosensory processes. We think that this connection has far reaching consequences beyond the somatotopic representation in the brain. As we will see below some studies suggest that vestibular information can alleviate pain, and we will also describe in more detail how it interfaces with affective processes.

[3]Known to activate predominantly the right hemisphere (Utz et al., 2010).
[4]Known to bilaterally activate vestibular cortical areas (Utz et al., 2010).

VESTIBULAR STIMULATION AND PAIN

Parents often comfort and sooth infants, when they just hurt themselves, by carrying and rocking them, thus providing plenty of vestibular stimulation (for scientific evidence for the soothing effect of rocking see e.g., Korner and Thoman, 1972; Byrne and Horowitz, 1981). The soothing effect may not be attributed to vestibular influences alone but so far—vestibular perception and pain—have rarely been combined in investigations although other sensory cues such as visual (Moseley et al., 2008a; Longo et al., 2009; Ramachandran et al., 2009) and tactile (Moseley, 2008; Moseley et al., 2008b; Moseley and Wiech, 2009) cues have been revealed to impact pain. The insular cortex is recognized as an important interoceptive center (Craig, 2009) and recent experiments suggest it might also provide a possible interaction between vestibular and nociceptive processing (zu Eulenburg et al., 2013b).

Pain is about protection of the body and chronic pain is associated with a range of disrupted bodily representations (for reviews see e.g., Moseley et al., 2012; Haggard et al., 2013). That vestibular stimulation attenuates similar disruptions raises the tantalizing possibility that it may also modulate pain. In fact, Harris hypothesized already in 1999 that CVS could relieve pain without accompanying tissue damage (e.g., phantom pain in an amputated limb). He hypothesized that pain arises as consequence of a mismatch between afferent sensory information and (motor) intention and that vestibular stimulation may help to restore balance in shared brain areas (Harris, 1999). Although there is limitated empirical support for the mismatch theory (e.g., Wand et al., 2014), there are a few studies reporting on the beneficial effect of vestibular stimulation. The first account that CVS can alleviate pain comes from participants with amputations and phantom limb perception (André et al., 2001). All of 10 amputees with painful phantom limb perception reported temporary relief after CVS (through the replacement with a normal non-painful phantom limb). Similar reports were made in two paraplegic patients with painful phantom limb perception (le Chapelain et al., 2001). The authors argue that vestibular information aids in reconstructing the global body schema (André et al., 2001), pinpointing the interaction between body representation and pain in these patients.

Shared brain structures for nociceptive and vestibular information processing have been proposed (for a review see Balaban, 2011). Recent clinical studies show yet again encouraging findings. Two patients with thalamic pain syndrome were suffering from severe pain in the contralateral body side after stroke for several years showing little relief from medication. Cold water CVS of the left and the right ear showed an important decrease in pain ratings, while sham stimulation had no effect. When the procedure was repeated just once, the positive effects lasted for several weeks (Ramachandran et al., 2007a,b). Nine patients with central post-stroke pain (CPSP; McGeoch et al., 2008) and one patient with transverse myelitis of the cervical

spinal cord who developed right-sided central pain (McGeoch and Ramachandran, 2008) received treatment with a similar CVS protocol. Again, overall pain ratings decreased significantly. Interestingly, these patients reported that pain relief was greatest in the upper body (face and arm) while there was only little relief for the lower body (leg). It has been hypothesized that the posterior insula and/or anterior cingulate cortex (ACC) play a key role in the neural underpinnings of pain alleviation induced by CVS. Vestibular stimulation activates the posterior insula, which in turn is proposed to inhibit the generation of pain in the ACC (Miller and Ngo, 2007; Ramachandran et al., 2007b; McGeoch and Ramachandran, 2008). This seems to be supported by the findings of a single-case study using MEG measurements before and after CVS revealing reduced ACC activation. This patient with CPSP reported decreased pain up to 4 days after treatment (McGeoch et al., 2009). Furthermore, results from three patients suggest that CVS can reduce pain only when the main vestibular cortical areas are spared (McGeoch et al., 2008; Rode et al., 2012). Given the low sample size in the studies reported above caution needs to be taken and the influence of potential biases will need to be controlled for in future research. In this context it is of interest that neurotransmitters can possibly help explain the beneficial effects of vestibular stimulation. Indeed, GVS was found to increase the release of GABA in rats (Samoudi et al., 2012) and gabapentin—a GABA analog—is a frequently prescribed drug to treat pain (e.g., neuropathic pain, Jensen et al., 2009).

Surprisingly, and to the best of our knowledge, there is only one study that has investigated whether vestibular stimulation can affect pain in healthy participants. Ferrè et al. (2013a) assessed tactile and pain thresholds in healthy participants before and after left-sided cold CVS. They showed that while tactile thresholds decrease, pain thresholds increased after stimulation, but no control condition was used, and the lack of a control intervention makes it hard to exclude diffuse noxious inhibitory control.

In sum, while these results are encouraging, more research with sound methodology (e.g., well-controlled studies that include sham conditions, randomized control studies) and greater sample size is needed. At this point it is still difficult to draw a conclusion whether the influences observed underlie a direct function or whether they are rather unspecific. Conceivable confounders may include stress (Saman et al., 2012), attentional or placebo effects. Moreover, future clinical studies need to clarify which chronic pain conditions can benefit from vestibular stimulation and which cannot. Moreover, which is the best vestibular stimulation protocol for which type of pain and what are the underlying neural underpinnings. While common vestibular and pain processing areas have been outlined, imaging studies yet need to assess possible structural changes due to vestibular stimulation. We hypothesize that vestibular stimulation can alleviate pain by contributing to ameliorate the impaired body schema and help restore the "body matrix" (Moseley et al., 2012). Thus, conditions like complex regional pain syndrome or chronic back pain, where disturbed body representations have been described (e.g., Moseley, 2005, 2008; Moseley et al., 2008a,b), should benefit the most. We even go on to speculate that other clinical conditions that involve disturbances of body representation such as Anorexia Nervosa (e.g., Garfinkel et al., 1978; Keizer et al., 2013) may profit as well. While Anorexia Nervosa has not yet been experimentally assessed and linked to vestibular stimulation, other mental disorders—outlined below—have been investigated. However, on this note, it is important to point out that a recent study that assessed the effect of CVS in participants suffering from body identity integrity disorder (BIID) was not able to significantly reduce the estrangement of the affected limb(s) (Lenggenhager et al., 2014). Against the background of publication bias, negative findings are informative and clearly indicate the need for well-controlled studies with sufficient sample size.

AFFECTIVE PROCESSES AND DISORDERS

Links between vestibular dysfunction, anxiety and panic disorders have been suggested for a long time (for an overview see Balaban and Jacob, 2001). Patients with a vestibular disorder have a higher probability of suffering from depression, anxiety and panic disorders (with and without agoraphobia) (Eagger et al., 1992; Godemann et al., 2004; Guidetti et al., 2008; Gazzola et al., 2009). Likewise, patients with a psychiatric disorder (such as anxiety or panic disorder) often report vestibular symptoms such as dizziness. A current model that explains the high comorbidity between psychiatric symptoms in vestibular disorders proposes that depression and anxiety are a reaction to the distress of living with vestibular dysfunctions (Jacob et al., 1996). This explanation does not provide any insights into the underlying mechanisms. Several studies concluded that patients with agoraphobic, panic or motion discomfort disorder have problems with multisensory integration (Yardley et al., 1994; Jacob et al., 1996, 1997). Vestibular patients rely predominantly on visual (Dieterich et al., 2007) and proprioceptive cues (Bles et al., 1984). Inadequate integration of visual and proprioceptive information may result in the fear of falling (*space and motion discomfort*) (Jacob et al., 1996). Interestingly, Viaud-Delmon et al. (2002) could show that participants with high trait anxiety also rely more on external visual cues in a visual-vestibular conflict task. The authors proposed that vestibular dysfunctions in high trait anxious participants may not affect low-level vestibular functions but rather involve problems with higher order cognitive integration of self-motion signals contributing to spatial cognition (Berthoz and Viaud-Delmon, 1999). However, previous studies show that low-level vestibular functions are also affected. Yardley et al. (1992) found an increased slow phase velocity of the VOR in high state anxious participants, which is an indicator for risk of dizziness. Studies in panic disorder patients have shown abnormal responses in postural stability and abnormal oculomotor functioning (Sklare et al., 1990; Redfern et al., 2007).

Taken together, epidemiological studies support a high comorbidity between vestibular and emotional disorders. However, the underlying neural mechanisms remain unclear. Although the limbic and prefrontal contributions to the processing of emotional information are well established, the influence of vestibular processes is not yet thoroughly understood. Recent evidence suggests that the interaction between vestibular functioning and

emotion processing may underlie shared subcomponents of a common neural network (Preuss et al., 2014a).

BRAINSTEM LINKS AND CORTICAL CONNECTIONS

Several brain regions are commonly involved in vestibular and emotion processing (Yardley et al., 1999; Balaban and Jacob, 2001). Widespread vestibular-cortical projections may account for the comorbidity between the vestibular and psychiatric symptoms (Balaban et al., 2011; Lopez and Blanke, 2011; Gurvich et al., 2013). One key anatomical region in the brainstem is the parabrachial nucleus (PBN; Balaban and Thayer, 2001; Balaban, 2004). The PBN provides a direct link between the vestibular system and emotion processing, and it has bi-directional connections to the vestibular nuclei (Balaban, 2002, 2004; Balaban et al., 2011). Furthermore, the PBN network exerts reciprocal connections to the amygdala, hypothalamus, locus coeruleus and prefrontal cortex, which are all areas of the limbic system and have been associated with affective disorders (Schuerger and Balaban, 1999; Gorman et al., 2000; Balaban and Thayer, 2001). Yet other brainstem regions that have reciprocal connections with the vestibular nuclei are the raphe nuclei and the locus coeruleus. Both regions are involved in psychiatric conditions. The raphe nuclei send serotonergic and nonserotonergic projections to the vestibular nuclei (Kalén et al., 1985; Halberstadt and Balaban, 2006) and axon correlates to the central amygdaloid nucleus, suggesting a modulating effect of vestibular pathways on affective control (Halberstadt and Balaban, 2006). The locus coeruleus sends noradrenergic projections to the vestibular nuclei (Schuerger and Balaban, 1999) and also responds to vestibular stimulation (Manzoni et al., 1989).

Within the vestibular network, the ACC has been considered as the bridge between vestibular-sensorimotor areas and the affect divisions of the prefrontal cortex that entail motivational states (Bush et al., 2000). The insular cortex is the core region that receives input from the vestibular nuclei in the brain stem (Akbarian et al., 1994). The prefrontal cortex plays a more indirect role in the processing of vestibular information and suppresses the impact of irrelevant sensory information and regulates incoming sensory stimulation that can overwhelm cognitive capacities (see for example Yamaguchi and Knight, 1990, 1991; Rule et al., 2002; Angrilli et al., 2008). For example, coherent full-field visual motion stimuli elicit the sensation of self-motion such as the illusory feeling of motion when sitting in the stationary train while it is only the neighboring train that pulls out of the station in the direction opposite to the felt motion. However, people react differently to full-field motion stimuli, and in laboratory experiments additional tasks can weaken the strength of vection (Seno et al., 2011). Prefrontal regions may exert their influence over the vestibular cortical regions through its indirect connection with the premotor areas and the temporal lobes (Damasio and Anderson, 2003). However, the prefrontal cortex does not only regulate incoming sensory information but it also serves the regulation of emotions. Indeed, Carmona et al. (2009) proposed a conceptual model, integrating both mechanisms and the role of vestibular information. The first mechanism ("sensorimotor-affective mechanism") involves the dense interconnection of the vestibular sensory areas and the anterior cingulate gyrus and the prefrontal cortex. Frontal regions (via motor areas and anterior cingulate gyrus) exert a regulatory influence on vestibular areas and attenuate sensory stimulation as described in the example given above (Carmona et al., 2009, see also Akbarian et al., 1994; Nishiike et al., 2000). The second mechanism ("autonomic-affective mechanism") involves the direct link between the vestibular nuclei with limbic structures. Carmona et al. (2009) propose that the frontal lobes exert an inhibitory control over the vestibular nuclei in the brainstem. As a consequence, intense negative stressors (triggered though vestibular dysfunctions, dizziness, disorientation, motion sickness etc.) burden frontal resources, resulting in diminished capacity to allocate resources for attenuating activation in posterior sensory and autonomic regions (e.g., the insula and the temporal lobe). This leads to difficulties in maintaining sensorimotor coordination in balance and regulating arousal.

VESTIBULAR STIMULATION, AFFECT AND LATERALITY

Recent evidence suggests that vestibular stimulation can have a positive effect on affect and psychiatric disorders. Dodson (2004) showed in a single case study that left cold CVS exerts a beneficial effect on manic symptom severity. The positive effect of CVS on mania can be attributed to an activation of right hemispheric structures. Levine et al. (2012) showed an increase in bilateral frontal and central alpha EEG band activation in three patients suffering from a schizoaffective disorder. They proposed that left cold CVS can have a short lived beneficial effect on manic delusions and insight of illness that appear in mania and other types of psychoses (i.e., schizophrenia).

Hemispheric laterality in the processing of emotions and affective information has been proposed for many years. Lateralization of vestibular processes, however, is relatively new and has come to light in the last years. Dieterich et al. (2003) could show a dominance of vestibular cortical function in the non-dominant hemisphere. Several studies reported greater right than left hemispheric activation in the vestibular cortex (Bottini et al., 1994, 2001; Dieterich et al., 1998, 2003; Lobel et al., 1998; Fasold et al., 2002; Kahane et al., 2003; Schlindwein et al., 2008). Models of hemispheric lateralization of emotions have proposed that the hemispheres process emotional information differently ("valence-specific hypothesis") (Tucker, 1981; Davidson and Fox, 1982; Davidson, 1992).

Although conversely discussed, the valence-specific hypothesis assumes that negative emotions are processed in the right hemisphere whereas positive emotions are processed in the left hemisphere. Pettigrew and Miller (1998) proposed a model for bipolar disorder ("sticky switch model"), which views mania as the endpoint of relative left hemispheric activation and depression as the endpoint of relative right hemispheric activation. In order to examine this hypothesis, Miller et al. (2000, 2003) used a binocular rivalry task in which two competing images are presented to each eye separately. This leads to an alternating perception of each image mediated by alternating hemispheric activation (*interhemispheric switching*). The author reported a slower alternation rate in patients with bipolar disorder leading to the conclusion of a slow *interhemispheric switching* in these patients—the brain becomes "stuck" in one of two states (Miller

et al., 2003). Interestingly, CVS can be used to effectively modulate the alternation rate in binocular rivalry (Miller et al., 2000).

The findings of these studies all lead to the conclusion that vestibular stimulation could be a potential therapeutic treatment in mania and depression. Left cold ear CVS, through its activation of the right hemisphere, was proposed to reduce manic symptom severity whereas right cold ear CVS, through its activation of the left hemisphere, was proposed to reduce symptoms in depression. Since then, clinical evidence has indeed shown a beneficial effect of left cold CVS on manic symptom severity (Dodson, 2004; Levine et al., 2012). So far, only one study investigated the effect of CVS in major depression (Ried and Aviles, 2007). Patients suffering from a major depressive disorder show a bilateral decrease in slow phase velocity of the nystagmus following 30°C and 44°C CVS. Unfortunately, changes in mood were not assessed. In addition to clinical findings, a recent study could show that CVS has mood and affect regulating effects in healthy participants (Preuss et al., 2014a). Preuss et al., 2014b could show that left cold CVS decreases affective control whereas right cold CVS increased affective control for positive stimuli in an affective Go/NoGo task. The authors concluded that the change in affective control is due to an activation of the underlying emotional network. Furthermore, a recent study could show that CVS can also influence decision outcome in purchase decision-making. Left cold CVS decreased the probability of purchasing a product and also desirability of the products (Preuss et al., 2014b). McKay et al. (2013) could show that cold CVS of the left ear decreases unrealistic optimism in healthy subjects. Unrealistic optimism is a bias that causes a person to believe that he or she is less at risk of experiencing negative events (such as illnesses). Hence, unrealistic optimism represents some sort of delusion or subclinical anosognosia in healthy subjects. Indeed, the authors conclude that both unrealistic optimism and anosognosia (see also Cappa et al., 1987) share the same underlying mechanisms. Future studies should thus further investigate the effect of CVS in affective disorders as CVS might regulate mood and affect in major depression and mania but also give insight into delusion and illness denial. Vestibular stimulation by non-invasive methods, and its potential use in the treatment of the conditions outlined above is by far not exploited.

DISCUSSION

Activation of the vestibular system leads to widespread activity in different cortical areas but the extent of all the functions the vestibular network is involved in are not yet clear. We have described three streams of research, which have in common that they can be modulated by vestibular information. None of these areas belongs to traditional domains of vestibular research like postural control, VOR, and self-motion perception. Therefore, the question about the purpose of vestibular information in these tasks is by all means justified. Before searching for answers to this question, one needs to take a step back and wonder why the answers are not yet known already. Several conceivable explanations can be brought forward. First, it is clear that the paucity of knowledge in a given field is proportional to the amount of research carried out. The number of 24,163 articles shows up in PubMed with the term "vestibular" in the title or abstract. In comparison, there are 261,164 with the term "visual" (PubMed, October 18th, 2013, the results are corrected for contributions with both terms). This means that there are 10.8 times more articles published in the visual domain. Indeed, the visual system processes a wider range of different stimuli such as motion, color, orientation, form and so forth, and to date, the knowledge of cortical neurophysiology is by far better understood when compared to the vestibular domain. It is a relatively recent trend that vestibular information has gained some more attention based on growing evidence of its involvement in tasks that are seemingly remote from known vestibular functions. Second, the lack of knowledge is—at least in part—caused by the experimental effort that is necessary to carry out vestibular experiments. For example, motion devices that are capable of providing well-controlled vestibular stimuli do not belong to the standard equipment of perception research laboratories. They are expensive and often require labor intense software development for machine control. Moreover, true motion cannot be applied in combination with most neuroimaging devices, and the use of techniques like CVS and GVS entail problems of inducing sensory conflicts (e.g., during CVS participants are in a pitched-back position and receive a stimulation of the canals while the otoliths signal no change in posture). A promising new technique for vestibular research is functional near-infrared spectroscopy (fNIRS) because participants can be tested in different body positions as compared to fMRI studies, which only allow measurements in the supine position. A recent fNIRS study by Karim et al. (2013) used CVS and confirmed previous fMRI and PET activation and lateralization patterns on the cortical surface. Last but not least, it is puzzling that sporadic research findings in vestibular science are not followed up more rigorously. A case in point is the work by Sauvan and Peterhans (1995) and Sauvan (1999). They have shown that a proportion of neurons in occipital area V2 shift their orientation specificity from retinal to gravity related coordinates during static roll tilts. This finding brings up fundamental questions about multisensory integration and the level at which otolith information is fed into the visual system to achieve space constancy. The striking phenomenon of a perceptually upright world when the head is tilted is not understood, but, currently, there seems to be relatively little interest in a thorough investigation of this fundamental spatial ability, also among the large community of vision scientists. To our knowledge, no follow-up study has been conducted since Peterhans and Sauvan's work, and only few articles made reference to their work.

What are the functions vestibular information can have in tasks that are seemingly remote from known functions like self-motion perception or postural control? First of all, the vestibular system establishes a frame of reference for spatial orientation. It provides information about the spatial relation of the self with respect to the world. Bringing the gravito-inertial force (GIF) vector in line with the body's main axis is the set value in any type of behavior. The GIF is an allocentric cue and its perception connects egocentric body-based coordinates with external world coordinates. Sudden and unintended deviations from the GIF are rapidly compensated for by postural adjustments. In case of obstacles a continued and undesired deviation from

the GIF indicates vulnerability and therefore distress, which is a warning signal and thus reinforces the motivation to initiate a change in posture. Disequilibrium is a stressor indicating an unintended mismatch between frames of reference. This is where the interface between balance and affective processes—both phylogenetically old mechanisms—comes into play. Affective processes signal importance, and trigger a more or less elaborated coping behavior, depending on the organism's capacities. In this sense, postural reflexes involve more than just a change in body posture. Disequilibrium and falls are a threat to the organism that triggers an affective response. In real life, it is possible that the body's immediate and fast reflex loops precede the affective response such as when we miss a step on the stairs without actually falling. We start to feel the increase in heart beat just after having successfully avoided a fall. The existence of this vestibulo-affective interaction will unfold to its maximum when immediate correction of posture is impeded. Affect and body motion are interconnected, and future research will be needed to explore the underlying mechanisms. Moreover, a bodily representation of the self, for example, serves as a reliable tool for mentally simulating future events without having to act them out. This representation can trigger affective responses because the representation constitutes the self. Vividly imagining a fall can cause fear and affective responses, just as in the real world walking down a steep slope on a frozen street inevitably causes fear of falling. Mental imagery does not only draw in an off-line mode on sensory representations but it also involves affective processes depending on the relevance of the imagined content.

This review highlighted the role of vestibular information beyond guiding the body through the physical world. Cognitive processes such as mental spatial transformations or the processing of spatially represented information is nested with the processing of vestibular information. These vestibular interactions with higher-order spatial cognition could be based on the reference frame that the vestibular system provides the brain with. The otolith organs constantly update our body position in space with respect to gravity and this allows for representing the outside world within defined spatial vectors (horizontal, vertical, and transversal axis). The same spatial reference system manifests itself in cognitive tasks. According to the grounded cognition theory, space as a more concrete domain is used to structure, represent, and understand abstract concepts such as number magnitudes or temporal events that cannot be experienced directly through our senses (e.g., Lakoff and Johnson, 1980; Boroditsky, 2000; Gallese and Lakoff, 2005; Barsalou, 2008).

The vestibular system is a phylogenetically old structure that is nested and intertwined with subcortical and cortical structures. On the one hand, some reflex arcs can be considered vestigial such as ocular counterrolling because it does not fully counteract the impact of head tilts on the retinal image. On the other hand, however, the same efferent signal driving ocular counterrolling may be involved in other processes such as determining the gain of the visual field influence on the perception of the visual vertical as proposed by Bischof (1974). The multiple connections with other systems make it extremely complex to tease apart when and how vestibular input affects the processing of other modalities or affective responses. It is interesting that the vestibular system alone might be less plastic when compared to other sensory systems (Hartmann et al., 2013). Merfeld (2012) pointed out that vestibular organs appeared very early in evolutionary history and have remained relatively unchanged. It is therefore conceivable that an increase in vestibular sensitivity as a result of perceptual learning could have negative side effects such as motion sickness or an exaggerated response to small accelerations, for example during transport, and changes in sensitivity might affect all other modalities that are connected to the vestibular system. In fact, there is evidence that the vestibular system has numerous connections and overlaps with other functional networks. Based on recent research in spatial cognition, body representation and affective processes we presented an overview that will hopefully stimulate and contribute to future research in vestibular science.

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Ways to investigate vestibular contributions to cognitive processes

Antonella Palla*[1] *and Bigna Lenggenhager*[1,2]

[1] *Department of Neurology, University Hospital Zurich, Zurich, Switzerland*
[2] *Zurich Center for Integrative Human Physiology, Institute of Physiology, University of Zurich, Zurich, Switzerland*
**Correspondence: bigna.lenggenhager@gmail.com*

Edited by:
Stephane Besnard, INSERM U1075, France

Reviewed by:
Pierre Denise, Université de Caen Basse-Normandie, France
Gaëlle Quarck, Université de Caen Basse-Normandie, France

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Originally conceived as a primary system embedded into reflex generation for spinal and ocular-motor control, there is now an exciting and rapidly growing line of research showing that the vestibular system—which is intrinsically highly convergent with other sensory and motor signals (Angelaki and Cullen, 2008)—interacts with various cognitive processes such as spatial navigation (Angelaki et al., 2009), space perception (Ferre et al., 2013a), body representation (Lopez et al., 2010; Ferre et al., 2013c), mental imagery (Lenggenhager et al., 2008; Falconer and Mast, 2012; Van Elk and Blanke, 2014), attention (e.g., Figliozzi et al., 2005), memory (e.g., Smith et al., 2010), risk perception (Mckay et al., 2013), and even social cognition (Lopez et al., 2013).

Insight in this area has mostly been gained through the use of standardized clinical equipment such as caloric, galvanic, and vestibular evoked myogenic potential (VEMP) devices. While these techniques bear several advantages, it is important to recall that they stimulate the vestibular organ in an unnatural and non-physiological way. Such artificial stimulation might be exploited for specific questions, but might hamper the investigation of others. Below we will briefly describe the advantages and disadvantages of various stimulation techniques for investigating specific research questions from cognitive neuroscience (see **Figure 1** for a summary). Emphasis will be put on those stimulation methods that best approximate natural movement, i.e., whole-body motion platforms. We will provide evidence that even though these highly sophisticated apparatus are technically demanding and hence not routinely available, they are indispensable for investigating certain vestibular-cognitive interactions.

WAYS TO STIMULATE THE VESTIBULAR SYSTEM

The most frequently used techniques for investigating vestibular influence on cognitive processes are caloric (CVS) and galvanic (GVS) vestibular stimulation (for CVS see e.g., Been et al., 2007;for GVS see e.g., Utz et al., 2010). Initially developed for clinical diagnostics, they now play an increasingly important role in cognitive neuroscience, mainly due to their safe, inexpensive, non-invasive and easy applicability. In addition, they have enthusiastically been proposed as a potential therapeutic method for various bodily, affective and cognitive disturbances (e.g., Ramachandran and Mcgeoch, 2007; Preuss et al., 2014). Yet, next to some technical limitations (e.g., co-activation of other sensory systems or side effects Lenggenhager et al., 2008), some peculiarities must be considered in order to appraise their value.

CVS induces an endolymphatic flow within the semicircular canals by creating a temperature gradient from one end to the other end of the canal (for details about the technique, see e.g., Fetter, 2010). It is usually applied in participants placed in a supine position with their head tilted 30° forward. This way the horizontal semicircular canals are gravitationally horizontal, and thus most strongly stimulated. By changing the orientation of the head, i.e., positioning one of the vertical semicircular canals gravitationally horizontal, these latter can also be targeted. The vestibular sensation induced by CVS is complex and comprises feelings of rotation along the frontal [i.e., coronal rather than axial (i.e., yaw)] plane, floating, tilting to either side, being elevated or pulled down (e.g., Kolev, 2001). Importantly, the complexity of vestibular sensations reflects the non-physiological nature of the stimulus.

GVS, on the other hand, is transmitted via two electrodes placed over the mastoid process. The behavioral response induced by GVS is also complex, including sensations of rocking, pitching, tilting, and rotations. This complexity most likely originates from the simultaneous stimulation of *all* peripheral afferents (Goldberg et al., 1984) including those of the semicircular canals and otoliths (Curthoys and Macdougall, 2012). The direction of vestibular sensation can be modulated depending on the current flow, being unidirectional when using direct current flow and bidirectional when using sinusoidal flow (e.g., Stephan et al., 2005).

Another frequently used stimulation technique in clinical setting is vestibular stimulation through brief pulses of air-conducted sound or bone-conducted vibration. Specifically, vibrations applied to the head, most commonly the forehead or the mastoid, are thought to cause small linear movements of the bone while intense sound induces flow of the

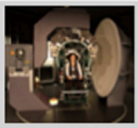
	CVS	GVS	VEMP	Rotatory motion stimulator	Linear motion stimulator
					
Predominately activated vestibular organ	Horizontal semicircular canals[a]	Otoliths and semicircular canals	Otoliths	Horizontal semicircular canals[b]	Otoliths and semicircular canals
Suitable for testing hemispheric differences	Yes	Yes	No	No	No
Suitable for testing temporal and spatial aspects	No	No	No	Yes	Yes

FIGURE 1 | Summary of the most common methods to stimulate the vestibular system and their suitability for testing specific cognitive research questions. [a]Typical subject position during CVS, predominantly stimulating the horizontal semicircular canals. Note that the vertical semicircular canals can also be stimulated by changing the subjects head position in order to place the vertical canals gravitationally horizontal. [b]Typical subject position on a custom-built rotatory chair with the subject placed such that their center of head rotation falls along the chair rotation axis. This type of rotation predominantly activates the horizontal semicircular canals. Note that the vertical semicircular canals and the otoliths can also be activated by displacing the subject's head out of the chair rotation axis (i.e., lateral displacement or tilting).

inner ear fluid through movements of the stapes. Both stimulations activate predominately otolith receptors, which are assessed by measuring electromyographic activity from the extraocular, via ocular VEMP, or sternoclaidomastoideus, via cervical VEMP. Yet, some authors argued for an additional semicircular contribution (Zhu et al., 2011). Notably, such stimulations have to our best knowledge not been used in cognitive research. Moreover, it is not known if and what sensations are exactly generated by VEMP stimulation, as up to know VEMPS have only been used to diagnose and confirm otolithic dysfunction (Rosengren et al., 2010).

Next to CVS, GVS, and VEMPs, motion stimulators are increasingly occupying an integral part in vestibular research. The pivotal advantage of motion platforms is that they provide complete quantitative information about the induced movement kinematics, including position, velocity, acceleration, and the dynamics. They can be programmed to approximate natural movements and the vestibular sensations generated can thus be closely related to the actual movement.

Custom-built rotatory chairs activate mainly the horizontal semicircular canals as the participant is usually sitting upright with the center of the head passing through the chair rotation axis (see also **Figure 1**). If the subject is positioned in supine, prone, or on the side, however, also the vertical semicircular canals can be stimulated. Otoliths can be activated when the center of the head is displaced eccentrically to the axis of chair rotation, e.g., by lateral displacement (centrifugal rotation) or by tilting (off-vertical axis rotation, OVAR). The behavioral response elicited by centrifugal rotation and OVAR is however also complex. The former induces a combined tilt-translation sensation such as being on a gondola while OVAR instead builds up a sense of as being translated along a circular trajectory (described as either feeling swayed around a cone during earth-vertical OVAR or as being translated around a circular path without the sense of turning, just like in a gondola of a Ferris wheel during earth-horizontal OVAR Vingerhoets et al., 2007). Finally, linear motion simulators equipped with six actuators allowing the motion and positioning in space following the 6° of freedom are now increasingly publicized for otolithic stimulation and already used in some laboratory. Yet, the frequency and displacement range is compared to rotatory chairs still limited. Unfortunately, such linear motion stimulators are not yet used for standard clinical testing and knowledge on vestibular induced sensations is scare.

"WHAT" AND "WHEN" TO STIMULATE THE VESTIBULAR SYSTEM

The vestibular activation patterns and corresponding sensations as well as the technical limitations of the various vestibular stimulators might importantly influence results and conclusions of neurocognitive research. By means of some exemplary studies, in the following we aim to provide suggestions on which vestibular technique should preferentially be considered for which type of cognitive research question.

We propose that the cognitive processes influenced by vestibular signals can roughly be gathered into two groups: (a) cognitive processes in which temporal and spatial aspects are important and (b) cognitive processes in which neural hemispheric asymmetries are important.

The cognitive processes with a clear spatial component include mental space representation such as the mental number line (Hartmann et al., 2012; Ferre et al., 2013b) and mental body transformation or perspective-taking (Lenggenhager et al.,

2008; Falconer and Mast, 2012; Van Elk and Blanke, 2014). Several studies have investigated whether vestibular sensations influence mental space and movement representations. In these studies, the consideration of the specific vestibular organ that is predominantly activated by the stimulator as well as the perceived direction of the induced movement is crucial. For instance, for addressing questions about *linear* mental space representation [e.g., in order to simulate motion along a number line in space (Hartmann et al., 2012)], the use of stimulators that activate the otoliths (i.e., GVS, VEMP[1], rotational or linear motion stimulators) might be the most appropriate. We believe however, that for the above-mentioned studies, linear motion simulators (if available) should be preferred over artificial stimulation as the cognitive task and the vestibular stimulation can be matched more precisely in space and time. This is particularly true as the percept induced by artificial stimulation is very variable among participants. Corroborating this assumption, Hartmann et al. (2012) showed by means of linear motion simulators that small number generation is facilitated during leftwards and large number generation during rightwards horizontal movements, whereas Ferre et al. (2013b) did not find any spatial bias on the mental number line using GVS. The use of motion simulation allowed Hartmann and colleagues (2012) to let participants generate the numbers during the peak of linear acceleration and to demonstrate that linear mental space is plane-related as they could not replicate their findings when exposing the participants to vertical plane stimulation. Such precise motion simulation in space as well as in time is not possible with artificial stimulation.

Similarly, the choice of vestibular stimulator could be important when investigating mental own body transformations in space (Lenggenhager et al., 2008; Falconer and Mast, 2012; Van Elk and Blanke, 2014). As these tasks require participants to mentally rotate their body[2], using stimulators that predominantly activate the semicircular canals (i.e., CVS or rotatory chairs) might be the most appropriate, since these best imitate a rotational movement. Again, differences in vestibular stimulation could presumably explain the discrepancies found between existing studies on this topic. For instance, while Lenggenhager et al. (2008) and Dilda et al. (2012) found a general and direction-unspecific slowing of mental own body rotation during GVS, Falconer and Mast (2012), using CVS, and Van Elk and Blanke (2014) using a rotatory chair reported direction-specific speeding up of mental rotation when the induced and the imagined rotation were congruent.

Whereas the great value of motion simulators consists in the ability to explore temporal and spatial processes of cognition and might thus be very important for future research investigating embodied and spatial cognition, they may be inferior as compared to CVS and GVS for the investigation of strongly lateralized (i.e., right or left cerebral hemispheric) cognitive aspects such as risk perception (Mckay et al., 2013) or emotion (Preuss et al., 2014). Vestibular stimulation has been showed to activate a large neural network, centered in multisensory areas of the temporo-parietal cortex and posterior insula (see e.g., Lopez and Blanke, 2011 for a recent review). Co-activation of shared neural networks might make vestibular stimulation an interesting tool for the manipulation of various cognitive tasks, similar to cortical stimulation techniques (e.g., tDCS or TMS). For this line of research, we would advise the use of CVS and/or GVS for two main reasons: First, both techniques revealed a hemispheric dominance of vestibular projections (i.e., stimulate preferentially one hemisphere depending on the stimulation pattern), making them interesting for testing interference with hemispheric specialization (Dieterich et al., 2003). Related to self-risk estimation and the hypothesis of asymmetrical brain processing, one could for example, expect stronger results with CVS than with rotatory motion stimulator, as the former activates cortical hemispheres more asymmetrically than the latter (for a CVS study see Mckay et al., 2013). Second, as for these studies, it is usually interesting to know which exact brain mechanism underlie the interaction, a further advantage of CVS and GVS is that they can easily be used in a scanner. While advantages in more mobile neuroimaging techniques (e.g., NIRS) might soon overcome this limitation, up to now there are no neuroimaging studies using real motion simulation.

CONCLUSION

In sum, artificial galvanic and caloric vestibular stimulation techniques are very useful and to date constitute a keystone in cognitive neuroscience. We argue however, that for certain specific research questions—mainly those assessing vestibular influences on spatial cognition—the use of more sophisticated motor stimulators is indispensable. Generally, we believe that the complexity of the vestibular system and the growing repertory of stimulation devices (and parameters) make a critical selection of the vestibular stimulation important. This paper aims to sensitize readers from the cognitive or from the vestibular domain to these aspects when designing an experiment and interpreting the data. We also hope that future papers in this field will more often include the underlying reasoning for choosing one over another technique.

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[1]Even if otolith stimulation through VEMPS do presumably not evoke any self-motion perception, it might be interesting to investigate its implicit influence on certain cognitive tasks.

[2]This is of course not the case when the mental transformation is linear, e.g., when simulating moving forward or backwar.

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The vestibular system: a spatial reference for bodily self-consciousness

Christian Pfeiffer[1,2], Andrea Serino[1,2,3] and Olaf Blanke[1,2,4]*

[1] *Center for Neuroprosthetics, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland*
[2] *Laboratory of Cognitive Neuroscience, Brain Mind Institute, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland*
[3] *Department of Psychology, Alma Mater Studiorum, University of Bologna, Bologna, Italy*
[4] *Department of Neurology, University Hospital Geneva, Geneva, Switzerland*

Edited by:
Stephane Besnard, INSERM U1075, France

Reviewed by:
Francesca Ferri, University of Ottawa, Canada
Hong Yu Wong, University of Tübingen, Germany

****Correspondence:***
Olaf Blanke, Department of Neurology, University Hospital Geneva, Rue Gabrielle Perret-Gentil 4, 1205 Geneva, Switzerland
e-mail: olaf.blanke@epfl.ch

Self-consciousness is the remarkable human experience of being a subject: the "I". Self-consciousness is typically bound to a body, and particularly to the spatial dimensions of the body, as well as to its location and displacement in the gravitational field. Because the vestibular system encodes head position and movement in three-dimensional space, vestibular cortical processing likely contributes to spatial aspects of bodily self-consciousness. We review here recent data showing vestibular effects on first-person perspective (the feeling from where "I" experience the world) and self-location (the feeling where "I" am located in space). We compare these findings to data showing vestibular effects on mental spatial transformation, self-motion perception, and body representation showing vestibular contributions to various spatial representations of the body with respect to the external world. Finally, we discuss the role for four posterior brain regions that process vestibular and other multisensory signals to encode spatial aspects of bodily self-consciousness: temporoparietal junction, parietoinsular vestibular cortex, ventral intraparietal region, and medial superior temporal region. We propose that vestibular processing in these cortical regions is critical in linking multisensory signals from the body (personal and peripersonal space) with external (extrapersonal) space. Therefore, the vestibular system plays a critical role for neural representations of spatial aspects of bodily self-consciousness.

Keywords: bodily self-consciousness, multisensory integration, first-person perspective, self-location, self-motion, mental spatial transformation, body representation, vestibular cortex

INTRODUCTION

Humans' experience as subject ("I", the self) is typically bound to the spatial dimensions of the physical body. This is expressed by the concept of bodily self-consciousness, which consists of several aspects including the experience that "I" am localized at a specific place and spatial volume (self-location), the experience that "I" take an experiential and visuospatial perspective of the world (first-person perspective), the experience that "I" identify with the body as a whole (self-identification) as opposed to feeling ownership for a body part, and that "I" am causing actions through the body (sense of agency) (Haggard et al., 2003; Jeannerod, 2003; Blanke and Metzinger, 2009; Blanke, 2012; Metzinger, 2013; Serino et al., 2013). This review will mainly focus on what we call spatial aspects of bodily self-consciousness, i.e., self-location and first-person perspective. These phenomenal experiences are defined by spatial parameters, such as the location and volumetric expansion of the self and the origin and direction of perspective (Blanke and Metzinger, 2009). In contrast, we will be less concerned with non-spatial aspects of bodily self-consciousness, i.e., self-identification and agency. These phenomenal experiences are invariant to changes in spatial parameters (see Metzinger, 2013 for a discussion on self-identification without a body in lucid dreams and during out-of-body experiences).

Experimental research shows that both spatial and non-spatial aspects of bodily self-consciousness emerge from pre-reflective and non-conceptual representations of bodily signals in the brain (Metzinger, 2003; Gallagher, 2005; Blanke and Metzinger, 2009; Ehrsson, 2012). Those are sensory signals from exteroception, such as visual and auditory signals (e.g., Ehrsson, 2007; Lenggenhager et al., 2007; Tajadura-Jiménez et al., 2009), from somatosensation, such as tactile and proprioceptive signals (e.g., Seizova-Cajic et al., 2007; Palluel et al., 2011; for reviews see Haggard et al., 2003; Serino and Haggard, 2010) and from interoception, such as cardiac, nociceptive, and thermal signals (Hänsel et al., 2011; Aspell et al., 2013; for an interoception-based account on consciousness see Craig, 2002, 2009). Altogether, these experimental studies imply that by integrating multisensory signals the brain generates a coherent spatial representation of body parts, the body as a whole, and the body as related to the external world.

However, much less is known about the role of the vestibular system for bodily self-consciousness. Because the vestibular

system encodes the position and movement of the head in three-dimensional space, and because in the central nervous system vestibular signals are strongly integrated with motor, visual, somatosensory and proprioceptive signals (Grüsser et al., 1990a,b; Gu et al., 2007; Prsa et al., 2012), central vestibular processing may be an important contributor to the neural computations underlying spatial aspects of bodily self-consciousness. Specifically, vestibular signals might contribute in generating a spatial representation of the body as a whole with respect to the external world, i.e., in the gravitational field in particular. These vestibular signals might be critical for updating whole body representation while this one moves in external space. Accordingly, the vestibular system would encode spatial references for self-location and first-person perspective.

This review summarizes and critically discusses both direct and indirect evidence for this proposal. While topics in the fields of bodily self-consciousness and central vestibular processing have been mostly studied in isolation, with this review article we hope to motivate a converging approach from these exciting research fields.

The review is divided in three parts. In the first part, we briefly introduce the vestibular system and then summarize current knowledge about the role of vestibular processing for spatial aspects of bodily self-consciousness. We conclude the first part by several questions that remain open to experimental research. In the second part, we review experimental data about vestibular contributions to cognitive and perceptual processes that involve spatial representations of the bodily self with respect to the external world. We think that these self-related processes draw on similar functional mechanisms as spatial aspects of bodily self-consciousness, and we discuss these experimental data as indirect evidence for vestibular contributions to spatial aspects of bodily self-consciousness. The third and final part of this review is concerned with the neural correlates of vestibular processing underlying self-location and first-person perspective. We propose that self-location and first-person perspective are encoded by a posterior cortical network consisting of the temporoparietal junction (TPJ), i.e., a region that has been causally linked to bodily self-consciousness, and three vestibular cortex regions, i.e., the parietoinsular vestibular cortex (PIVC), the medial superior temporal region (MST), and the ventral intraparietal region (VIP), which together perform the necessary computation subserving a multisensory spatial reference for bodily self-consciousness. We discuss the known functional properties of these regions and their putative role in bodily self-consciousness. Together we provide an argument supporting our hypothesis and present a testable outlook for future research for the study of vestibular processing in spatial aspects of bodily self-consciousness.

PART ONE: THE VESTIBULAR SYSTEM AND BODILY SELF-CONSCIOUSNESS: CURRENT KNOWLEDGE AND OPEN QUESTIONS

THE VESTIBULAR SYSTEM

The vestibular system encodes linear and rotatory acceleration of the head. It senses constant linear acceleration by earth gravity and thus signals to the brain head movement and position with respect to a constant gravitational acceleration. The vestibular system contributes to a variety of central nervous system functions including motor control, e.g., stabilizing gaze by the vestibular-ocular reflex (Schwarz, 1976), body posture (Pozzo et al., 1990), perception, e.g., of verticality (Lopez et al., 2007), and of self-motion (Brandt et al., 1998). Moreover, it also contributes to cognition, e.g., spatial navigation and memory (Arthur et al., 2009), and bodily self-consciousness (Blanke et al., 2002; Pfeiffer et al., 2013), which is the main topic of this review.

Peripheral system

The peripheral vestibular organs are located bilaterally in the head and are part of the inner ear (**Figure 1A**). They consist of two otolith organs (utricle and saccule) that sense linear acceleration, e.g., by head motion or gravitational force, and three semicircular canals (anterior, posterior and horizontal canal) that sense rotational acceleration around three cardinal axes (yaw, roll, pitch, **Figure 1B**). Thus, the vestibular sensory organs encode head position and movement in three-dimensional space.

Experimental research on the vestibular system has mainly used two approaches in order to stimulate the vestibular system, i.e., by natural and artificial stimulation. Natural vestibular stimulation can be experimentally induced by head accelerations, e.g., by passive whole-body rotation or translation (e.g., Prsa et al., 2012; van Elk and Blanke, 2014) that are sensed by the semicircular canals or otolith organs respectively. Natural vestibular stimulation may be given under terrestrial conditions by constant gravitational forces due to the attraction exerted by the earth on mass. Because the otolith organs sense constantly the vector of constant acceleration by gravity, static body or head tilts with respect to gravity can be used to naturally stimulate the otolith organs. The effects of weightlessness on vestibular processing have been studied in spacecrafts in orbit or in aircrafts during prolonged free fall (i.e., up to several months duration) or during parabolic flight (i.e., less than a minute duration).

Artificial peripheral vestibular stimulation techniques are: monopolar or bipolar electrical stimulation at the mastoids (Galvanic Vestibular Stimulation, GVS), thermal irrigation of one or both ear canals (Caloric Vestibular Stimulation, CVS), and auditory stimulation on headphones (clicks and short-tone bursts). These stimulation techniques activate the semicircular canals, otolith organs, the vestibular nerve, or a combination of the previous. Notably, these artificial stimulations co-activate nociceptive, thermal, and auditory sensory receptors—for comparison of these techniques and cortical processing see Lopez et al. (2012b).

Vestibular cortex

The central nervous system vestibular pathway consists of: (i) vestibular nerve projections from the vestibular organs to the vestibular nucleus in the brainstem; (ii) projections from the brainstem to thalamic nuclei, cerebellum, and spinal cord; and (iii) projections from the thalamus to the cerebral cortex. The interested reader can find comprehensive reviews on the peripheral and central vestibular system in Goldberg et al. (2012) and Lopez and Blanke (2011).

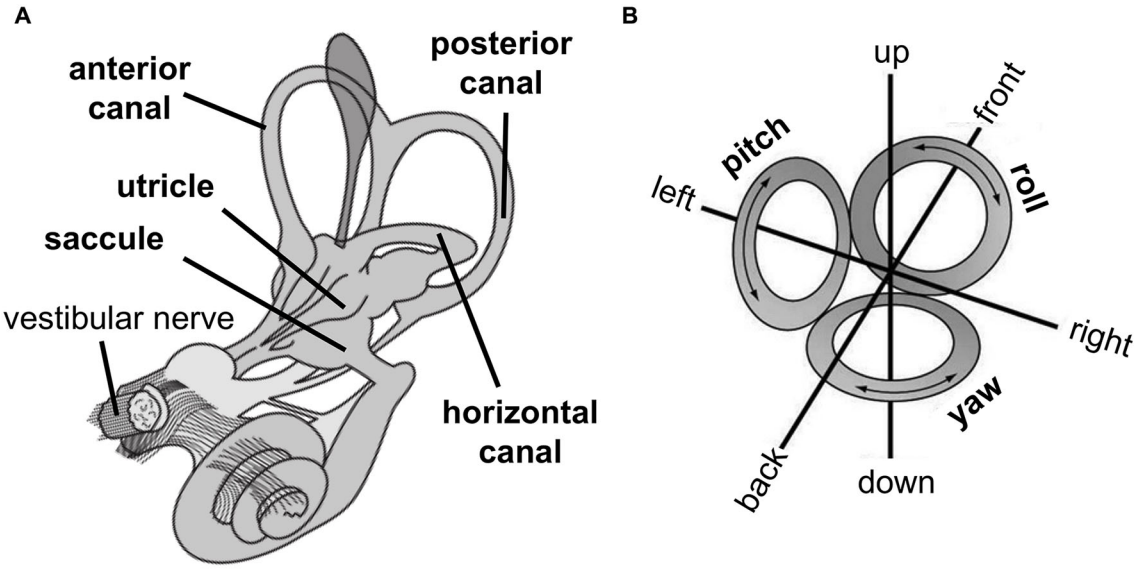


FIGURE 1 | (A) Peripheral vestibular organs in the inner ear consist of otoliths, i.e., utricle and saccule, which sense linear acceleration, and semicircular canals, i.e., anterior, posterior, and horizontal canal, which sense rotational acceleration. The vestibular nerve projects signals from otoliths and semicircular canals to the central nervous system. **(B)** The vestibular system encodes movement in three-dimensional space denoted as linear movements, i.e., in front, back, left, right, up, and down direction (by otolith organs) and rotational movements, i.e., yaw (by the horizontal canal) and pitch and roll (by both anterior and posterior canal). (Images are derivatives of works by NASA, licensed under creative commons.)

While for vision, audition, and somatosensation specific unisensory primary cortices have been identified, no such unisensory vestibular cortex seems to exist in the human brain. Rather, vestibular cortex is considered as any cortical region receiving vestibular input from the thalamus and is a distributed cortical network that overlaps with multisensory and motor representations from vision, somatosensation, proprioception, and action (Lopez and Blanke, 2011).

Electrophysiological recordings in non-human primates have identified vestibular inputs in several cortical regions including the somatosensory cortex (area 3aN, area 3aH, area 2v), PIVC, dorsal MST, medial temporal cortex, frontal cortex (frontal eye field and supplementary eye field), and cingulate cortex (Grüsser et al., 1990b; Guldin et al., 1992; Bremmer et al., 2002; Gu et al., 2007). These recordings revealed therefore thalamocortical projections to all major cortical lobes except the occipital lobe.

In order to measure human vestibular cortical processing, many studies have used functional magnetic resonance imaging (fMRI). While fMRI has the advantage of high spatial resolution and non-invasiveness, it is worth noting that studying vestibular processing in fMRI has several limitations. First, participants are required to lie supine and must avoid head movements, which differs from conditions of vestibular stimulation in natural context, typically involving different head postures and movements. Secondly, in order to stimulate the peripheral vestibular organs artificial stimulation techniques (GVS, CVS, clicks) are used. These co-activate other sensory modalities and complicate the interpretation of observed brain activation as purely vestibular Lopez et al. (2012b). Finally, the static magnetic field of the MR scanner induces a constant vestibular stimulus that, depending on participant's head position, differently activates the vestibular sensory organs and can even induce vertigo (Mian et al., 2013). Thus, there are limitations with current fMRI approaches to study central vestibular processing. It will be an important future goal to develop novel approaches allowing more natural and specific vestibular stimulation during non-invasive neuroimaging in humans.

VESTIBULAR CONTRIBUTIONS TO BODILY SELF-CONSCIOUSNESS

Theory

It has been proposed that bodily self-consciousness is based on the brain's multisensory integration of visual, vestibular, somatosensory, proprioceptive and motor signals (Haggard et al., 2003; Blanke et al., 2004; Blanke and Mohr, 2005). This theory distinguishes between personal (including also peripersonal) space, which is a volume of space occupied by the physical body and the space immediately surrounding the body, and extrapersonal space, that is the space outside of personal space. The theory proposes that the vestibular system is critically involved in integrating sensory signals from personal space (e.g., somatosensory, proprioceptive, visual, and auditory signals) with sensory signals from extrapersonal space (e.g., visual and auditory signals). It was proposed that particularly otolithic vestibular signals about constant gravitational acceleration provide a world-centered reference for the bodily self. By means of multisensory integration between personal and extrapersonal space the brain generates a spatial representation of the body as a whole, with a given location and orientation with respect to the external world, i.e., bodily self-consciousness. In line with this theory, Lopez et al. (2008) argued that vestibular otolithic signals are highly relevant for spatial aspects of bodily self-consciousness, i.e., self-location and first-person perspective, which depend on signals from both personal

and extrapersonal space, and that vestibular signals may be less relevant for non-spatial aspects of bodily self-consciousness, e.g., self-identification, which depend mainly on signals from personal space and relate mostly to the body itself, rather than to the body relative to the external world (see also Blanke, 2012).

Clinical data

The strongest support for the proposal that vestibular processing contributes to bodily self-consciousness comes from observations in neurological patients suffering from out-of-body experience who show a three-way disembodiment of their bodily self-consciousness (Devinsky et al., 1989; Blanke et al., 2002, 2004; Brandt et al., 2005; De Ridder et al., 2007; Ionta et al., 2011; Pfeiffer et al., 2013). During an out-of-body experience patients typically identify with an illusory body in external space (disembodied self-identification), feel to be elevated above their physical body (disembodied self-location), and to have an elevated visuospatial perspective directed back downward to the physical body (disembodied first-person perspective).

Out-of-body experience in some neurological patients were caused by damage (Ionta et al., 2011), dysfunction (Blanke et al., 2004), or electrical stimulation (Blanke et al., 2002) at the TPJ, i.e., a brain region that receives strong vestibular inputs (Lopez et al., 2008, 2012b; zu Eulenburg et al., 2012). In addition to out-of-body experiences, electrical stimulation at TPJ also induced vestibular, visual, and kinesthetic hallucinations (Blanke et al., 2002). Vestibular processing and out-of-body experience were linked at the phenomenal level in a different study on healthy individuals. Cheyne and Girard (2009) found that humans suffering from sleep paralysis (i.e., a sleep disorder that is associated with immobility after awakening from sleep) often experienced vestibular-motor hallucinations as well as out-of-body experiences. According to self-report these experiences occurred mostly in supine posture and began mostly with vestibular-motor hallucinations that were followed by out-of-body experiences.

Out-of-body experiences most frequently occur in supine posture when otolithic vestibular signals are altered with respect to the vertical body axis (Green, 1968), suggesting that otolithic vestibular processing is critical for these changes in bodily self-consciousness (Lopez et al., 2008). Together, these reviewed data suggest that altered vestibular processing at temporoparietal cortex is associated with disturbances in bodily self-consciousness during out-of-body experiences.

Experimental data

Similar changes in bodily self-consciousness can be studied in healthy humans using different body illusions, such as the body-swap illusion (Petkova and Ehrsson, 2008), the out-of-body illusion (Ehrsson, 2007) or the full-body illusion (Lenggenhager et al., 2007). During a classic version of the full-body illusion (Lenggenhager et al., 2007) a participant views (from a third-person viewpoint) a virtual body being stroked at the back, i.e., visual stroking, and simultaneously feels stroking at his or her physical body, i.e., tactile stroking. Importantly, the visual stroking of the virtual body and the tactile stroking at participant's physical body are spatially separated. Synchronous visuotactile stroking typically increases self-identification with the virtual body and increases self-location in the direction of the virtual body, when compared with an asynchronous stroking control condition (comprehensive reviews and comparison to similar illusions in Blanke, 2012; Serino et al., 2013).

Using such a full-body illusion setup we recently showed that the subjectively experienced direction of first-person perspective, together with self-location, was altered by directional conflict between otolithic vestibular and visual gravitational signals (Ionta et al., 2011; Pfeiffer et al., 2013). **Figure 2** shows the experimental setup and results. Participants viewed a virtual body from an elevated visuospatial viewpoint, seeing visual gravity in downward direction, and simultaneously lay in supine body posture, receiving otolithic vestibular signals about their body being upward directed relative to gravity. Under these conditions individuals differed in terms of their experienced first-person perspective: up-group participants experienced an upward-directed first-person perspective and an upward-directed change in self-location during the full-body illusion. In contrast, down-group participants experienced a downward-directed first-person perspective and downward-directed change in self-location. Interestingly, individual differences in first-person perspective and self-location were reflected in changes in neural processing, as revealed by fMRI, in the bilateral TPJ, or more precisely in the posterior superior temporal gyrus (pSTG), a region close to the lesion overlap found in a group of patients with out-of-body experiences, i.e., angular gyrus (Ionta et al., 2011).

Pfeiffer et al. (2013) found at the behavioral level that individual differences in the subjective first-person perspective depended on individual differences in the way individuals weight visual and vestibular information, as assessed by subjective visual vertical judgments (Oltman, 1968). Participants oriented a visual line with respect their subjective vertical. A tilted frame around the line induced a small bias in subjective visual vertical judgments in some of the participants (visual independent group), while inducing larger subjective visual vertical biases in other subjects (visual dependent group). We found that assignment of participants to visual field dependent-independent groups, depending on their performance in the visual vertical judgment task, was predictive of their subjective first-person perspective during the full-body illusion. Specifically, participants from the visual independent group more likely experienced an up-looking first-person perspective during the full-body illusion, meaning that their subjective first-person perspective was congruent with vestibular signals. On the other hand, participants from the visual dependent group were more likely to experience a down-looking first-person perspective during the full-body illusion, meaning that their subjective first-person perspective was in line with visual signals.

Together, these studies support the hypothesis that the vestibular system contributes to whole-body spatial representation underlying bodily self-consciousness (Blanke et al., 2004; Blanke, 2012). One may wonder whether also body-part spatial representations depend on vestibular signals. Indeed, body-part representations are related to whole-body representations (Petkova et al., 2011; Ehrsson, 2012) and several studies observed vestibular effects on touch localization and shape perception of the hand

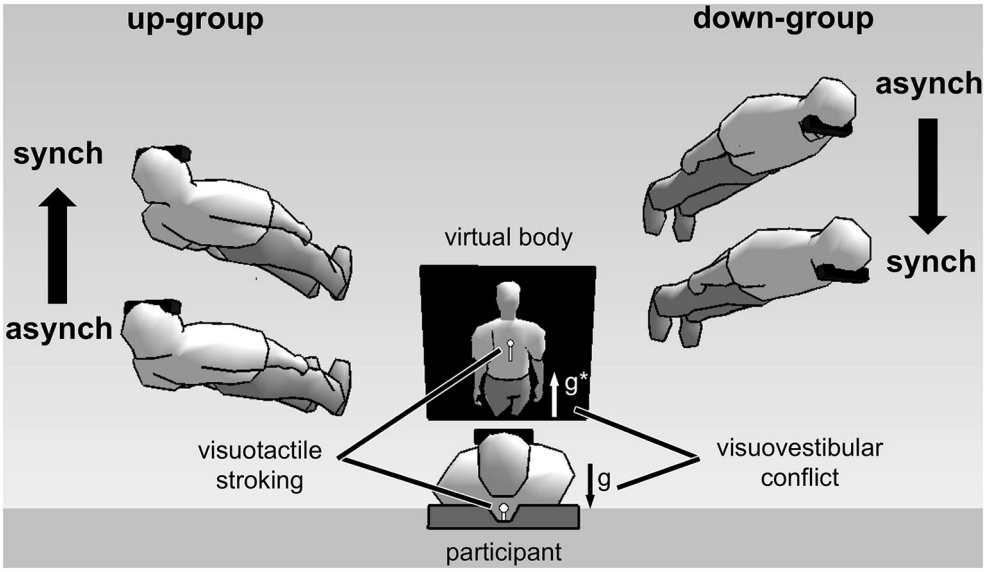


FIGURE 2 | Experimental setup and results of full-body illusion experiments using visuovestibular and visuotactile conflict (Ionta et al., 2011; Pfeiffer et al., 2013). (Image center shows) A participant in supine posture views a virtual body on a head-mounted display. Vestibular otolithic signals about gravity (g) are in opposite direction with respect to visual gravitational signals (g*)—thus in visuovestibular conflict. Results showed individual difference in first-person perspective experience. Virtual bodies at the left side of the figure represent subjective experiences made by up-group participants. These participants experienced an upward first-person perspective and showed congruent upward change in self-location during synchronous (synch) as compared to asynchronous (asynch) stroking condition. The opposite pattern was observed for down-group participants (shown at the right side of the figure).

(Lopez et al., 2010, 2012a,c; Ferre et al., 2011, 2013). However, these studies did not test whether vestibular stimulation also affected spatially integrated whole-body representations that underlie spatial aspects of bodily self-consciousness.

PART ONE: CONCLUSION AND OPEN QUESTIONS

Multisensory conflicts, i.e., between vestibular otolithic and visual gravitational signals in healthy subjects, as well as vestibular hallucinations, i.e., due to functional interference at TPJ in neurological patients, have been associated with changes in bodily self-consciousness, most consistently regarding it's spatial aspects: first-person perspective and self-location. Phenomenal experiences during these illusions included vestibular hallucinations, i.e., illusory reversals of the visuospatial first-person perspective with respect to gravity. Furthermore, ambiguous visual gravitational and vestibular otolithic signals induced changes of both first-person perspective and self-location. These observations suggest a critical role of vestibular cortical processing underlying spatial aspects of bodily self-consciousness.

Yet, very little is known about the functional and neural mechanisms underlying these effects. For instance, the vestibular peripheral system was never been directly stimulated during an out-of-body experience and a full-body illusion. It is thus not well studied how otolithic, semicircular, or both signals together affect spatial aspects of bodily self-consciousness. Furthermore, little is known about how vestibular processing contributes to a volumetric representation of the body, and how this spatial volume is related to representations of the external world. Finally, the vestibular system signals movement of the head and of the body. However, most studies on spatial aspects of bodily self-consciousness have used static body conditions. We think that these are important research questions for the future.

PART TWO: VESTIBULAR CONTRIBUTIONS TO BODILY SELF-RELATED COGNITIVE AND PERCEPTUAL FUNCTION

The second part of the review summarizes empirical research showing vestibular effects on mental spatial transformation, self-motion perception, and body representation. These cognitive processes involve spatial representations of the body, the external world, and the relationship between body and external world. We argue therefore that bodily self-related processes closely resemble spatial aspects of bodily self-consciousness, which require volumetric representation of the body with respect to the external world and spatial reference frames.

MENTAL SPATIAL TRANSFORMATION

Mental spatial representations are an important aspect of self-conscious experience. For example, the capacity to take the visual perspective of other humans is important for spatial cognition (Maguire et al., 1998), theory-of-mind (Baron-Cohen et al., 1985; Saxe and Kanwisher, 2003; Frith and Frith, 2006) and bodily self-consciousness (Newen and Vogeley, 2003).

Mental spatial representations have been extensively studied by mental imagery tasks involving objects, body parts, or entire bodies at different locations and orientations in external space (Shepard and Metzler, 1971). Mental imagery of these objects involves mental spatial transformation without participants actually moving their body or the perceived object. Performance

in these tasks, i.e., reaction times and error rates, generally depend on the object rotation angle and the shortest path of rotation (Shepard and Metzler, 1971; Parsons, 1987a; Wexler et al., 1998). Mental imagery of body parts or entire bodies additionally depends on anatomical constraints of the physical body (Parsons, 1987b, 1994) and on participant's body posture while performing the mental imagery task (Ionta and Blanke, 2009; Ionta et al., 2013).

A long tradition in cognitive neuroscience has studied egocentric imagery, which is self-centered mental spatial transformation of the own whole body or visuospatial perspective. In egocentric imagery tasks participants judge spatial attributes of objects in their environment from a location or perspective that differs from their actual location or perspective. For example, participants may judge whether a marker is at the left or right side of their imagined body location. Some researchers referred to egocentric imagery in the context of body-part imagery (Zacks and Michelon, 2005) which we argue does not necessarily draw on global representations of the whole body, but rather depends on body-part centered reference frames (Klatzky, 1997; Blanke, 2012). Therefore, we choose to refer to egocentric imagery for imagined own whole-body or perspective transformations. Egocentric imagery is typically compared to allocentric imagery, which is imagining transformations of objects in external space in order to judge their spatial attributes. Several studies have shown that egocentric vs. allocentric imagery depend on distinct functional neural activations (Mast et al., 1999; Wraga et al., 2005). For instance, egocentric, but not allocentric, imagery exhibits brain activity at the TPJ (Arzy et al., 2006)—the same brain region involved in spatial aspects of bodily self-consciousness, in out-of-body experience (Blanke et al., 2002, 2004; Blanke and Mohr, 2005) and in full-body illusions (Ionta et al., 2011).

While most previous research comparing egocentric with allocentric imagery focused on visual, motor, and proprioceptive contributions, more recent studies have shown very specific contributions of vestibular signals to egocentric mental spatial transformation. For instance, Grabherr et al. (2011) compared mental imagery in patients with vestibular loss (i.e., peripheral vestibular damage) with performance of healthy individuals (i.e., intact peripheral vestibular system). These authors found that bilateral vestibular impairment affected egocentric imagery when compared with unilateral loss or intact vestibular processing. Vestibular damage vs. intact vestibular processing did not affect allocentric imagery, thus highlighting the relevance of peripheral vestibular signals (intact or semi-intact) in egocentric imagery. Notably, egocentric imagery is known to rely on cortical activation of the TPJ (see above).

Likewise, highly specific effects of vestibular processing on egocentric imagery were found by Lenggenhager et al. (2008). Healthy participants received vestibular stimulation by left/right anodal GVS while viewing left/right rotated bodily or non-body object. Egocentric imagery was facilitated by side-congruent vestibular-visual stimulation, but only if participants viewed bodily objects. GVS had no effect on allocentric imagery and did not influence mental imagery of non-body objects. These results not only show vestibular modulation of egocentric imagery, but also vestibular processing specifically affecting body-related mental transformations for multisensory congruent directions. These results are congruent with clinical observations linking vestibular, visual, and kinesthetic processing at the TPJ and with changes of spatial aspects of bodily self-consciousness during out-of-body experience (Blanke et al., 2002).

While Grabherr et al. (2011) and Lenggenhager et al. (2008) studied the effects of vestibular damage and artificial stimulation on mental imagery, van Elk and Blanke (2014) used natural vestibular stimulation and found comparable results. Passive whole-body yaw rotations (activating the horizontal semicircular canals) facilitated egocentric body-related mental imagery if actual rotations and shortest paths of mental rotation were side-congruent. While general bilateral vestibular loss in the study by Grabherr et al. (2011), and GVS in the study by Lenggenhager et al. (2008), involved altered vestibular signals from both otoliths and semicircular canals, the study by van Elk and Blanke (2014) showed that selective stimulation of the semicircular canal signals affected egocentric mental imagery.

These data indicate that mental spatial transformation depends on vestibular signals. Vestibular processing enhances egocentric imagery when related to a visually seen bodily object. Vestibular signals from semicircular canals and otolith organs facilitate mental imagery in a spatial direction specific fashion.

Given that egocentric mental imagery draws on similar spatial representations and neural processing as spatial aspects of bodily self-consciousness, then it is likely that vestibular signals from semicircular canals contribute to spatial aspects of bodily self-consciousness and that they are processed at TPJ. To our knowledge, this hypothesis has not been studied directly. Instead, previous work on spatial aspects of bodily self-consciousness studied the effects of otolithic vestibular signals and representations of the static gravitational field.

Egocentric imagery recruits functional neural activation at the TPJ, suggesting that egocentric imagery engages similar representations, as do spatial aspects of bodily self-consciousness. Indeed, the strategy during egocentric imagery involves mental spatial displacement of one's own body or perspective to a location in external space, whose analogous physical movements would activate otolithic and semicircular canals respectively. The effects found for rotational-direction specific contributions of vestibular signals to egocentric imagery suggest that cortical processing of semicircular canal signals may contribute to spatial aspects of bodily self-consciousness. Finally, vestibular signals facilitates egocentric imagery when viewing a human body shape, suggesting that egocentric imagery and spatial aspects of bodily self-consciousness are highly tuned to visual representations of the human body.

SELF-MOTION PERCEPTION

Most everyday activities imply bodily movement in the environment. Planning and controlling these actions require accurate self-motion perception with respect to the environment and for this the brain must be able to monitor body movements based on multisensory signals. Furthermore, self-motion perception is important for balance, walking, and tracking the motion of objects under the influence of gravity. Research

has shown that self-motion perception depends on integrating redundant sensory signals about body movement from vestibular, visual, proprioceptive, auditory and kinesthetic signals. Although vestibular signals alone indicate head posture and movement with respect to the environment, they are poor at sensing very slow movements (Kolev et al., 1996) and prolonged constant-velocity movements (Brandt et al., 1998). Similarly, the otoliths cannot distinguish between linear acceleration from head motion and constant gravitational acceleration (Einstein, 1907). Research on self-motion perception studied therefore multisensory integration mechanisms, i.e., most extensively visual-vestibular integration, in non-human primates (Andersen et al., 2000; Bremmer et al., 2002; Gu et al., 2007; Bremmer, 2011). These studies found that in the non-human primate brain the medial temporal region and dorsal MST region integrate optokinetic stimuli and vestibular signals about head rotation and heading direction. Another area integrating vestibular, visual, and somatosensory signals relevant for self-motion perception is VIP (Bremmer et al., 1999; Chen et al., 2013a). Neuroimaging in humans found comparable activation for visual-vestibular integration for self-motion in posterior parietal, parietooccipital, and medial temporal regions (Brandt et al., 1998; Kleinschmidt et al., 2002; Kovács et al., 2008; Becker-Bense et al., 2012).

While these studies showed that self-motion perception depends on an optimal comparison of dynamic multisensory stimuli, including vestibular signals about bodily movement, more recent studies have shown that also constant gravitational acceleration signals are important for self-motion perception. For instance, De Saedeleer et al. (2013) found that under normal terrestrial conditions (with constant gravitational acceleration acting in the downward direction), the velocity of perceived self-motion depends on the spatial direction of visual implied motion, and that self-motion velocity perception shows an asymmetric pattern for upward vs. downward, but not for leftward vs. rightward motion. Specifically, visual self-motion is experienced as slower when directed upwards (opposite to the downward direction of gravitational acceleration) than when directed downward (in the same direction as gravitational acceleration). In microgravity, when no otolithic vestibular signals are present, this upward-downward asymmetry is abolished. Interestingly, the transition between asymmetric to symmetric perceptual bias is delayed by several days when astronauts in microgravity are presented with tactile cues that mimic foot sole pressure, as if they were standing upright in a gravitational field. These results suggest that constant gravitational acceleration, but also multisensory cues, affect self-motion perception.

Neural correlates of self-motion perception as related to the gravitational field have been studied by Indovina et al. (2013). During fMRI, these authors presented visual self-motion cues in a virtual rollercoaster. For motion in the vertical, but not in the horizontal, direction the PIVC region was activated—a key region in the cortex receiving vestibular inputs. The activation depended on motion acceleration constant and showed strongest activation for direction-acceleration congruent motion at earth-gravity constant 9.81 m/s^2.

Several studies from the same research group have previously shown that an internal model of gravity is recruited for visual motion perception. An internal model of gravity during these tasks recruited activation at of PIVC region, which was similarly activated by peripheral vestibular stimulation (McIntyre et al., 2001; Indovina et al., 2005). More recently, Maffei et al. (2010) found that visual object motion with a gravitational acceleration profile activated insula cortex and inferior parietal cortex. Both visually seen motion and unseen apparent motion cues similarly activated these regions. Activations were stronger when these signals were behaviorally relevant during an object interception task as compared to passive observation.

These recent studies in human subjects showed that self-motion perception is not only based on dynamic signals about body movement, but also on vestibular signal about the static gravitational field. Behavioral responses and functional neuroimaging suggest that the brain accounts for the effects of gravity on self- and environmental object motion by using an internal model of gravity that was found to overlap with cortical processing of vestibular signals in the PIVC region (Indovina et al., 2005, 2013)—a key region for vestibular input to the cortex (see Section Part Three: Vestibular Cortex and Spatial Aspects of Bodily Self-Consciousness of this review). Together, these findings suggest that vestibular signals about movement and position of the head are critical for self-motion perception, which draws on spatially representing one's own-body movements with respect to the external environment.

Experiments on self-motion perception have extensively inquired about participants' subjective experience of whether or not, and in which direction, they experienced to be moving. These are self-related perceptual judgments that are likely based on multisensory spatial representations of the bodily self ("I") and the external world. Thus, self-motion perception likely draws on similar neural representations underlying the spatial aspects of bodily self-consciousness, i.e., self-location and first-person perspective. It is important for the brain to spatially update self-location and first-person perspective while the body is in motion, and to withhold from spatial update when there is motion in the environment. However, research on bodily self-consciousness has mostly studied static body conditions and thus to date the exact relationship between functional and neural representations of self-motion perception and spatial aspects of bodily self-consciousness is not well understood.

BODY REPRESENTATION

Spatial aspects of bodily self-consciousness include a volumetric spatial representation of the body. Yet, no single sensory modality in isolation encodes such volumetric body representation. Instead, the brain integrates multisensory, body-related signals from the somatosensory, proprioceptive, visual, and, as it has been shown more recently, the vestibular system.

Longo and Haggard (2010) developed a task to assess perception of hand shape. They found that hand shape judgments were deformed in a manner partially resembling the cortical representation of the hand in primary somatosensory cortex. Using a similar task, Lopez et al. (2012c) studied the effect of vestibular stimulation by CVS on body representation and found that hand size judgments were generally enlarged by vestibular stimulation. A different study by Ferre et al. (2013)

applied vestibular stimulation by GVS during a homologous task and found that finger representations were enlarged while hand dorsum was shrunk by vestibular stimulation. The specific differences between the results in these studies, i.e., enlargement or shrinkage of hand shape judgments, may reflect differences in the spatial directionality of the vestibular signals applied. Specifically, vestibular stimulation by CVS mostly activates the horizontal canals that encode yaw rotation, whereas GVS activates mostly the vertical canals (i.e., anterior and posterior canals) that encode roll and pitch rotation (Lopez et al., 2012b). Alternatively, these results may be based on additional factors to the stimulation technique utilized; for instance, sensory co-activation of thermal and nociceptive sensory signals. Despite differences between studies, both findings show that vestibular stimulation deforms hand shape representation. Thus, in addition to visual, somatosensory and proprioceptive signals (Serino and Haggard, 2010), the brain also integrates vestibular signals in order to determine the volumetric representation of the body.

Vestibular stimulation temporarily altered participant's perception of the internal spatial configuration of the hand in the studies by Lopez et al. (2012c) and Ferre et al. (2013). These results differ from experienced changes of hand location during the rubber hand illusion (Botvinick and Cohen, 1998). Specifically, participants experience their own hand at a location different from their physical hand, but do not experience changes of hand shape. It seems that vestibular signals differently contribute to human position sense of implicit hand representations and overall hand location in external space. Two studies provide indirect support for this idea by showing that vestibular stimulation during the rubber hand illusion did not affect proprioceptive drift (Lopez et al., 2010, 2012a).

Generally, adult physical bodies undergo little change of shape over time, but vestibular stimulation immediately affected the internal representation of the hand shape. This suggests that highly plastic mechanisms underlie volumetric representations of the body. Such representations may be critical for spatial aspects of bodily self-consciousness, which can be manipulated rapidly during full-body illusions.

PART TWO: CONCLUSION

We reviewed data showing that vestibular signals from otolith organs and semicircular canals, as well as internal models of gravity, contribute to cognitive, sensorimotor, and perceptual functions. These self-related functions depend on vestibular processing at the TPJ, the intraparietal sulcus, the parietal-occipital and the medial temporal cortices. Because the TPJ also encodes spatial aspects of bodily self-consciousness, it is likely that vestibular processing at the TPJ is involved in both self-related processes and spatial aspects of bodily self-consciousness.

Vestibular signals are special sensory signals because the peripheral vestibular organs are fixed with respect to the head and therefore signal head movement relative to the external environment. Vestibular signals are thus likely to contribute in locating and updating location during movement of the body in the external world. However, vestibular signals alone are not sufficient, as they are signaling head position, but not the position of other body parts with respect to the external world. A multisensory integrated global representation of the whole body is necessary for bodily self-consciousness and thus vestibular signals need to be integrated with other spatially informative multisensory signals from the body. A full body representation can be achieved only by integrating multisensory body-related signals within a unique body-centered reference frame. Together vestibular world-related signals, when integrated with multisensory bodily signals, can provide a representation of the volumetric spatial body and its momentary position and orientation in space. Such representation of the whole body in space must be dynamically updated as the body and its parts continuously move. In this function, the vestibular signals are important to signal self-motion and thus to update spatial aspects of bodily self-consciousness with respect to the environment.

We think that for these functions, i.e., the spatial relationship between external world and a global full-body representation, and the update of the body-environment relationship in motion, vestibular processing in posterior brain regions is critical. In the final part of the present review we will present evidence supporting this view.

PART THREE: VESTIBULAR CORTEX AND SPATIAL ASPECTS OF BODILY SELF-CONSCIOUSNESS

What are the neural correlates of vestibular processing contributing to bodily self-consciousness? Empirical data shows that in the right hemisphere posterior cortical regions process both vestibular signals and spatial aspects of bodily self-consciousness (Dieterich et al., 2003; Blanke and Mohr, 2005; Ionta et al., 2011). In the third part of this review we summarize the functional characteristics of three important posterior vestibular cortex regions, i.e., PIVC, MST, and VIP, and a region causally involved in bodily self-consciousness, i.e., TPJ, which together may encode self-location and first-person perspective.

PIVC

It is commonly accepted that PIVC is a key region of vestibular input into the animal cortex (Grüsser et al., 1990a,b). This area also receives somatosensory and proprioceptive inputs (Lopez and Blanke, 2011). There is no consensus about the exact location and function of the PIVC in the human cortex. Different authors localized PIVC in the posterior insular and retroinsular cortex (Fasold et al., 2002; Indovina et al., 2005; Lopez et al., 2012b), in the parietal operculum (zu Eulenburg et al., 2012) and in different regions in the TPJ (Bense et al., 2001; Deutschländer et al., 2002; Lopez et al., 2012b). The available functional neuroimaging data in humans show that PIVC encodes vestibular signals from artificial stimulations by GVS and CVS (Fasold et al., 2002; Lopez et al., 2012b), proprioceptive signals from the neck (Fasold et al., 2008), and also visual signals (Brandt et al., 1998; Bense et al., 2001; Brandt et al., 2002; Deutschländer et al., 2002; Indovina et al., 2005, 2013). Although from non-human primate electrophysiology there is evidence for visual processing in PIVC (Grüsser et al., 1990a) there are also reports of no visual encoding in this region (Chen et al., 2010). Brandt et al. (1998) proposed that human PIVC and parietal occipital region encode visual and vestibular signals related to self-motion by a reciprocal

visual vestibular inhibition mechanism. Specifically, these authors proposed that vestibular input activates PIVC and simultaneously deactivates parietooccipital region. Optokinetic stimulation, on the other hand, would activate parietooccipital region and simultaneously deactivate PIVC. Accordingly, the dynamic interaction between activation and inhibition from PIVC to parietooccipital region and *vice versa* would allow for determining self-motion. The PIVC projects to all other vestibular cortex regions, which is why some authors have discussed PIVC as the main vestibular input region to the human cortex (zu Eulenburg et al., 2012).

What could be the role of PIVC in encoding the spatial aspects of bodily self-consciousness? Because PIVC can be considered a subregion of the TPJ (see **Figure 3**), on top of the evidence for PIVC as a major input area of vestibular signals into the cortex, in addition to PIVC's strong connection to pSTG region, the PIVC seems to be critical in encoding vestibular signals contributing to self-location and first-person perspective. During experimentally induced changes in self-location and first-person perspective, vestibular otolithic signals play a critical role (Ionta et al., 2011) and these otolithic inputs as well as internal models of gravity have been reported to be encoded by PIVC and immediately neighboring regions (Indovina et al., 2005). It is thus likely that PIVC encodes body orientation and motion in the gravitational field and that these signals interact with neural processing regions at the TPJ coding for spatial aspects of bodily self-consciousness. Determining a clear functional and anatomical localization of PIVC in humans and its distinction from other neighboring regions involved in bodily self-consciousness will be an important goal for future research.

MST

In non-human primates, the dorsal MST region is located in the extrastriate cortex. It processes visual optic flow stimuli, in addition to vestibular signals from body translation and rotation (Bremmer et al., 2002; Gu et al., 2007). Recent models proposed that MST neurons process the perceptual decision about self-motion by integrating visual and vestibular cues according to a Bayesian optimal integration model (Tanaka et al., 1986; Duffy and Wurtz, 1991; Gu et al., 2008; Fetsch et al., 2013; Chen et al., 2013a). While in primates next to MST also VIP neurons process optic flow, both regions are different in terms of their reference frame encoding such vestibular signals. While VIP encodes vestibular signals in body- and world-centered coordinates, MST encodes vestibular signals in eye-centered coordinates (Chen et al., 2013a,b). These data suggest that in primates, MST is a critical region of visuovestibular integration and self-motion perception. Due to morphological changes of the cortical structures between non-human primates and humans, the exact human homologue

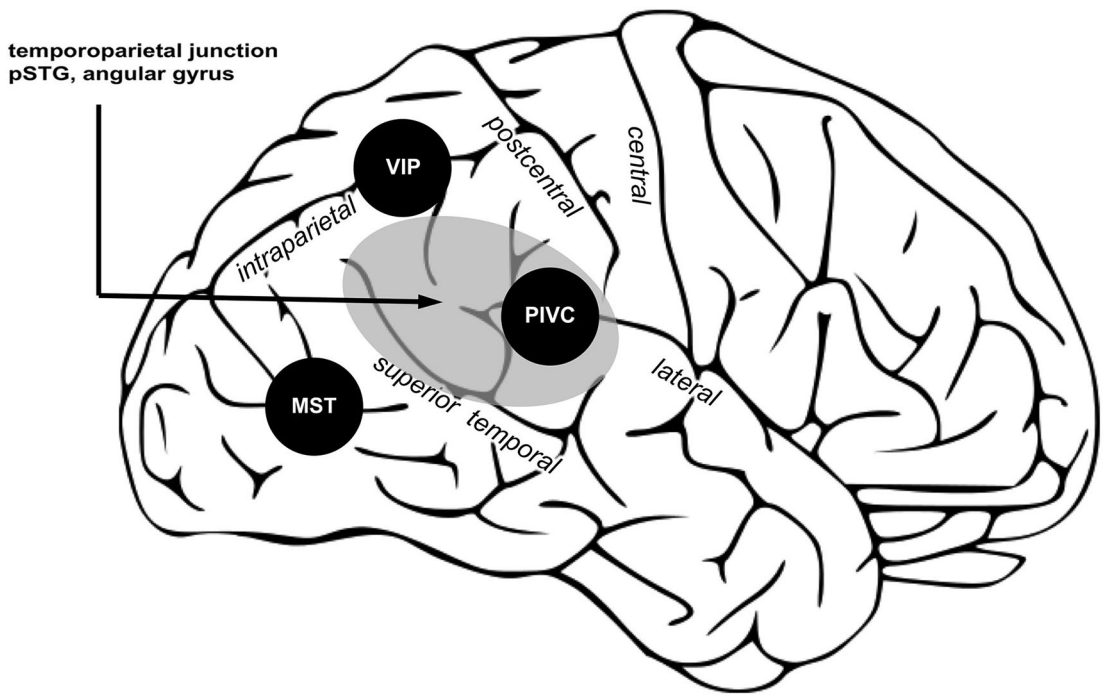


FIGURE 3 | Three posterior cortical regions processing vestibular signals are proposed important for bodily self-consciousness. PIVC encodes vestibular signals about position and movement of the head; VIP, integrates multisensory signals and computes reference frames transformation to common body and world-centered spatial reference frames; MST integrate vestibular and visual signals necessary for self-motion perception. Area in gray shows the TPJ, an area causally involved in encoding spatial aspects of bodily self-consciousness. Within TPJ, the pSTG and angular gyrus are regions associated to changes in spatial aspects of bodily self-consciousness in out-of-body experience and full-body illusion, and also the vestibular cortex region PIVC is part of the TPJ. (Image is a derivative of work licensed under creative commons.)

of MST (in terms of functional properties) is not precisely located in the human, however, functional neuroimaging studies have shown optic flow induced activity in the parietooccipital region (Brandt et al., 1998, 2002; Deutschländer et al., 2002). It is likely that the human homologue of MST is contributing to spatial aspects of bodily self-consciousness during self-motion by integrating visuovestibular signals. Therefore, vestibular processing in MST may play an important role in updating self-location and first-person while the body is in motion.

VIP

VIP is a critical region for multisensory spatial coding. First of all, several findings both in humans and animals show that VIP processes visual, tactile, proprioceptive, and auditory stimuli (Duhamel et al., 1997, 1998; Bremmer et al., 2001; Avillac et al., 2005; Schlack et al., 2005; Sereno and Huang, 2006; Huang et al., 2012). A main function of VIP neurons is to integrate spatial information from different sensory modalities, which initially encode space in peripheral sensory system centered coordinates (e.g., visual stimuli in retinotopic coordinates; auditory stimuli in head coordinates; somatosensory stimuli in somatotopic coordinates) into common body-centered reference frames. Most neurons in area VIP respond selectively to visual stimuli presented close the animal's body. Indeed, about half of VIP neurons respond best to visual stimuli within 30 cm of the body, and many neurons respond only within a few centimeters range (Colby et al., 1993). However, more distant space is also represented in VIP, since some neurons have visual receptive fields that are not confined in depth. In most neurons in VIP visual stimuli are encoded in body-part centered reference frames (typically centered at the head), some neurons are encoded in visual (retinal) reference frames, and some neurons have mixed reference frames (Avillac et al., 2005). Therefore, most VIP neurons preferentially represent the space near the body, in body-centered reference frames (Colby et al., 1993; Bremmer et al., 2002; Schlack et al., 2005). Although some neurons in VIP also encode visual-based representations of extrapersonal space, these extrapersonal space representations and the body-centered spatial representations are implemented in rather distinct neural populations within VIP (Colby et al., 1993), which supports the idea of distinct representations for near and far space, rather than a continuous representation from near to far space.

Interestingly, VIP also receives vestibular input. For instance, linear translations of the body, that are signaled by the otoliths, are encoded in VIP in body- or world-centered reference frames (Chen et al., 2013a). VIP may thus integrate vestibular with multisensory signals to compute spatial representations of the whole body—which are an important aspect of self-location (Blanke and Metzinger, 2009; Blanke, 2012; Metzinger, 2013). For all these reasons, computational models have proposed that VIP plays a critical role in coordinates transformation (Pouget et al., 2002; Avillac et al., 2005) and suggest that this region, together with other portions of the posterior parietal cortex plays a key role in remapping multisensory body-related signals into a common, whole-body centered, reference frames. Such computation is necessary to build a multisensory representation of the body in space, which is critical for spatial aspects of bodily self-consciousness.

TPJ

The TPJ can be defined as a larger region including the pSTG, angular gyrus, supramarginal gyrus, and the parietal operculum (**Figure 3**, gray region). The TPJ receives somatosensory, visual, and vestibular inputs (zu Eulenburg et al., 2012; Bzdok et al., 2013). Note that PIVC is a subregion of the TPJ (Lopez and Blanke, 2011; Lopez et al., 2012b). The TPJ is important for multisensory signal coding (Downar et al., 2000), theory of mind (Saxe and Kanwisher, 2003), and bodily self-consciousness (Blanke, 2012). Several findings presented in the first and second part of this review show that damage or stimulation at the TPJ can induce changes in self-location and first-person perspective (Blanke et al., 2002, 2004; Ionta et al., 2011). In the same vein, changes in self-location and first-person perspective, induced in healthy subject by the full-body illusion, are encoded at the TPJ, and in particular in the pSTG region. Thus, the TPJ seems to be a critical region for encoding spatial aspects of bodily self-consciousness. We think that vestibular inputs from PIVC, MST, and VIP to the TPJ are critical for that function. In particular, TPJ might integrate inputs from VIP contributing to a global body representation, from MST to update body orientation and direction during movement, from PIVC for the orientation of the body in the gravitational field. When these vestibular inputs are absent or in conflict with other sensory signals, e.g., visual or somatosensory, the brain may generate an inaccurate spatial representation of the bodily self, inducing illusions in healthy participants or disorders of bodily self-consciousness in patients.

CONCLUSION

The vestibular system processes head posture relative to constant gravitational acceleration and head motion in three-dimension space, thus providing important information related to the body with respect to the earth gravitational system, which is essential for coding the spatial orientation of the body in the external world. By reviewing recent data about bodily illusions, mental spatial representations, self-motion perception, and body representation, we argue that vestibular information is integrated with other sensory modalities to underlie bodily self-consciousness. Visual-vestibular interactions and internal models of gravity are processed at the TPJ, contributing to self-location and first-person perspective. We propose that this information depends on neural processing in the posterior cortical areas, which integrates and computes multisensory signals to build body representations in global whole-body centered reference frames and therefore contributes to stable representations of the bodily self. Integration of vestibular signals in PIVC, MST, and VIP, and further processing at the TPJ might be critical for the experience of the self as placed within a body, which occupies a specific location of space and faces the world from the first-person perspective. Vestibular processing may thus serve as a spatial reference for these spatial determinants of bodily self-consciousness.

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The relationship between vestibular function and topographical memory in older adults

Fred H. Previc[1]*, Wesley W. Krueger[2], Ruth A. Ross[1], Michael A. Roman[1] and Gregg Siegel[1]

[1] *Biomedical Development Corporation, San Antonio,TX, USA*
[2] *Ear Institute of Texas, San Antonio, TX, USA*

Edited by:
Stephane Besnard, INSERM U1075, France

Reviewed by:
Jocelyne Ventre-Dominey, INSERM, France
Marie-Laure Machado, U 1075 COMETE UCBN/INSERM, France

***Correspondence:**
Fred H. Previc, Biomedical Development Corporation, 620 East Dewey Place, San Antonio, TX 78212, USA
e-mail: fprevic@sbcglobal.net

Research during the past two decades has demonstrated an important role of the vestibular system in topographical orientation and memory and the network of neural structures associated with them. Almost all of the supporting data have come from animal or human clinical studies, however. The purpose of the present study was to investigate the link between vestibular function and topographical memory in normal elderly humans. Twenty-five participants aged 70 to 85 years who scored from mildly impaired to normal on the Montreal Cognitive Assessment (MoCA) received three topographical memory tests: the Camden Topographical Recognition Memory Test (CTMRT), a computerized topographical mental rotation test (TMRT), and a virtual pond maze (VPM). They also received six vestibular or oculomotor tests: optokinetic nystagmus (OKN), visual pursuit (VP), actively generated vestibulo-ocular reflex (VOR), the sensory orientation test (SOT) for posture, and two measures of rotational memory (error in degrees, or RM°, and correct directional recognition, or RM→). The only significant bivariate correlations were among the three vestibular measures primarily assessing horizontal canal function (VOR, RM°, and RM→). A multiple regression analysis showed significant relationships between vestibular and demographic predictors and both the TMRT (R = 0.78) and VPM (R = 0.66) measures. The significant relationship between the vestibular and topographical memory measures supports the theory that vestibular loss may contribute to topographical memory impairment in the elderly.

Keywords: vestibular, topographical memory, hippocampus, Alzheimer disease, elderly

INTRODUCTION

The topographical orientation system, also known as the spatial navigation, topokinetic, and action-extrapersonal systems, is one of the four major networks in the brain governing our interaction with our 3D environment (Previc, 1998). It is believed to be comprised mainly of three posterior regions—the hippocampus, posterior cingulate, and parietal-temporal cortex (Berthoz, 1997; Previc, 1998)—and frontal-striatal structures such as the caudate nucleus (Maguire et al., 1998). It is the system that is responsible for scene and route memory, presence in the world, and topographical orientation in the plane of the Earth's surface (Previc, 1998).

The most widely studied of the topographical regions is the hippocampus. Activation of the hippocampus occurs during recall of topographical routes (Maguire et al., 1997), and damage to it results in a profound amnesia for spatial landmarks, loss of spatial maps, and severe topographical disorientation (Aguirre and D'Esposito, 1999). In maintaining a cognitive map of the environment, the hippocampus integrates inputs from various sensory modalities, the two most important of these being distal visual inputs representing large regions of mainly the upper visual field (Previc, 1998; Arcaro et al., 2009) and those emanating from the vestibular system. In recent decades, a large literature has emerged concerning the role of vestibular inputs to the hippocampus (see Smith, 1997, for an early review). Aside from a few studies with humans (e.g., Vitte et al., 1996; Brandt et al., 2005), the evidence for a major role of the vestibular system in hippocampal function has come from animal studies involving vestibular stimulation or lesions (e.g., Ossenkopp and Hargreaves, 1993; Horii et al., 1994; Sharp et al., 1995; Russell et al., 2006; Tai et al., 2012). The primary labyrinthine inputs to the hippocampus and the topographical memory system in general are from the lateral/horizontal semicircular canals (Taube et al., 1996), which signal angular rotation of the head in the plane of the Earth's surface (i.e., the domain of the topographical as opposed to gravitational orientation system). The hippocampus also receives inputs from the utricle (Cuthbert et al., 2000), which signals linear acceleration in the plane of the Earth's surface. The importance of the vestibular inputs to the hippocampus may be due to the fact that the head is the anchor for the topographical memory system (Previc, 1998)—hence, the reference to it ("heading") when describing movements in topographical space.

Despite the above links, there is no clear evidence that vestibular function is related to topographical memory in normal humans. The purpose of this study was to assess the relationship

between various measures of vestibular and related oculomotor function and topographical memory in a sample comprised of cognitively and physically "normal" elderly participants (70–85 years). This age group was selected because of the recent hypothesis that declining vestibular function in the elderly may be associated with the onset of Alzheimer's disease (Previc, 2013), which is heralded by a loss of topographical orientation and memory and atrophy and/or metabolic deactivation of key components of the topographical neural network (Huang et al., 2002; Johnson et al., 2005; Berti et al., 2010; Pengas et al., 2012; Lithfous et al., 2013). Because it has proven difficult to test individuals with dementia to determine the presence of vestibular loss, the present study tested ostensibly "normal" older individuals to determine any relationship between subtle topographical memory loss and vestibular function.

To test topographical memory, three tests were used: the Camden Topographical Recognition Memory Test (CTRMT), a computerized topographical mental rotation test (TMRT) similar to the "four mountains" test used by Bird et al. (2010) and Hartley and Harlow (2012), and a virtual version of the widely used Morris water maze used in animals (Sharma et al., 2010) and humans (e.g., Moffat and Resnick, 2002; Brandt et al., 2005). While the CTRMT has not been specifically linked to hippocampal function, scene memory in general has been linked to the hippocampus (Epstein and Kanwisher, 1998; Arcaro et al., 2009; Bonnici et al., 2012). Memory for scenes requiring topographical mental rotation is also dependent on the hippocampus (Hartley and Harlow, 2012), and the critical role of the hippocampus in the water maze has been repeatedly shown in both animals (Sharma et al., 2010) and humans (Brandt et al., 2005). The standard vestibular and oculomotor tests used in this study, some of which have been linked to cognitive impairment in Alzheimer's disease (Previc, 2013), included visual pursuit (VP), optokinetic nystagmus (OKN), the actively generated vestibulo-ocular reflex (VOR), the sensory orientation test for postural control, and two measures of rotational memory—perceived rotation error in degrees and correctly perceived direction of rotation.

The relationships among the various topographical and vestibular measures were explored using a combination of correlational and multiple regression analyses.

METHOD

PARTICIPANTS

A total of 25 individuals between the ages of 70 and 85 (M = 76.37, SD = 4.47) participated in this study. The sample consisted of 16 females and 9 males. Nine of the 25 participants were of Hispanic origin and 21 were Caucasian, with 3 Asian-Americans and 1 designated "other". In terms of education, there were 7 participants with high school degrees, 6 with undergraduate degrees, and 12 with graduate degrees. All participants were prescreened for dementia, with anyone scoring less than 19 on the Montreal Cognitive Assessment (MoCA) excluded from the study. The MoCA scores ranged from 19 to 28 (M = 24.88, SD = 2.42).

All participants were prescreened for any previous balance or vestibular problems, and only two had any previous vestibular problems, both involving single episodes of dizziness or vertigo many years previously (These two participants each scored within one standard deviation of the mean or above on five of six "vestibular" tests, with one scoring low on VP gain and the other scoring low on the postural test—see later descriptions). Although no tests of visual function were performed, no participant reported difficulty in seeing any of the stimuli during the various tests. Anyone with neck surgery or hip replacement surgery was excluded, although knee replacements were permitted if they were not within the past year and were not causing the person any pain. Other exclusionary criteria included a history of brain trauma (including stroke, seizures, or traumatic brain injury), a diagnosed neurological condition, or current use of psychoactive drugs. Caffeine use not exceeding three cups of coffee or its equivalent per day, moderate social consumption of alcohol, and use of nonnarcotic pain medication was acceptable for inclusion into the study.

TESTING SITES AND EQUIPMENT

All spatial memory testing was performed in the neuropsychology office of Dr. Michael Roman in San Antonio, TX and required approximately 90 min. Two of the tests created for this study were computerized versions of previously used tests—the virtual pond maze (VPM), which tested spatial navigation and memory, and the topographical mental rotation test, which required participants to remember the original view of a scene and then rotate it mentally. Both of these tests were executed using a Hewlett-Packard Compaq NC6400 computer under moderately dim illumination with the participant seated in a quiet room. The third spatial memory test was the CTRMT, which was administered from a test booklet by the neuropsychologist sitting directly across from the participant in a well-lit room.

The "vestibular" tests were conducted at the Ear Institute of Texas clinic in San Antonio, TX and required slightly less than one hour on average to complete. The OKN, VOR, and VP tasks were all administered using the Vorteq system (Micromedical, Chatham, IL). This system contains an inertial head-tracker for measuring the motion of the head in space and an infrared camera for measuring the position of each eye in the orbit. These tests were all conducted in darkness, aside from illumination of the stimuli, and were preceded by a calibration of the system using the fixation stimulus positioned at five positions on the screen (center and 21.8° right, left, up and down, at a viewing distance of 160 cm). The Sensory Orientation Test (SOT) tested balance under various sensory conditions and made use of the Equitest system (Neurocom, Portland, OR). Finally, the rotational memory test was administered on a barber-style chair locked in place on a rotating industrial turntable whose motion was controlled electronically (Carousel, Monrovia, CA). The turntable had an accuracy of ∼0.5° for the profiles and velocities and displacements used in this study (25°/s; up to 40° left or right). When seated in the chair, which was centered on the turntable, the participant was situated at the approximate radius from a large white circular Mylar half-screen (diameter = 155 cm) containing a scale that measured laser-pointing accuracy to 0.5°.

TESTS

Camden Topographical Recognition Memory Test (CTRMT)

This task required participants to view photographs of 30 urban scenes, presented according to the standard instructions (Warrington, 1996) in which participants viewed each scene for up to 3 s and had to determine if the photograph was shot by an amateur or a professional. Immediately after the completion of the presentation sequence, participants were shown each of the same 30 scenes in a different order along with two similar versions of it shot from different perspectives or poses. In this three-alternative self-paced forced-choice recognition task, participants were required to point to the scene that was actually presented and to avoid guessing. Each score was based on the total correct out of 30.

Topographical Mental Rotation Test (TMRT)

Participants viewed a scene containing a set of three objects (e.g., red cylinder, blue sphere, green cube) and were then shown a figure instructing them to rotate their viewpoint 90° left, 90° right, or 180° opposite (see **Figure 1**, left panel). They were then shown three scenes from each of the viewpoints and asked to use the mouse to click on the image that depicted the correct viewpoint shift. A yellow box indicated their choice while a green box (only presented during practice trials) showed the correct viewpoint. Participants had 12 s to view each scene and 14 s to make their response, with a timer appearing during the last 5 s of the forced-choice interval. After being presented with instructions, which included demonstrations with actual objects, participants viewed a set of 12 practice trials (they could view a second set if they chose to) and then were presented with 15 test trials. Each score was based on the total number of correct responses out of 15.

Virtual Pond Maze (VPM)

In the pond maze, participants started from one of six locations around a virtual pond. Each starting location faced a different set of virtual buildings and vegetation to provide distinct spatial landmarks (see **Figure 1**, right panel). Participants were required to navigate using only the left and right cursor arrows to a fixed platform slightly offset from the middle of the pond, with the forward speed set by the software at a simulated 7 m/s. The location and size of the platform was set such that participants had to make at least one correction to reach the platform from each of the starting points. After approximately 20 min of instructions and practice, participants were tested on 18 trials, consisting of one platform-visible trial followed by two platform-nonvisible trials, in which spatial memory was required to reach the platform. Performance on the 6 visible and 12 nonvisible trials was measured by the time taken to reach the platform, the virtual distance traveled, and the number of corrections made. The starting position on each trial varied in a random-without-replacement order, such that all starting positions were sampled twice in the nonvisible conditions and once in the visible conditions. Because the number of corrections involved more strategy than memory and the virtual distance was almost perfectly correlated with time to reach the platform, only the latter was used in the final analysis.

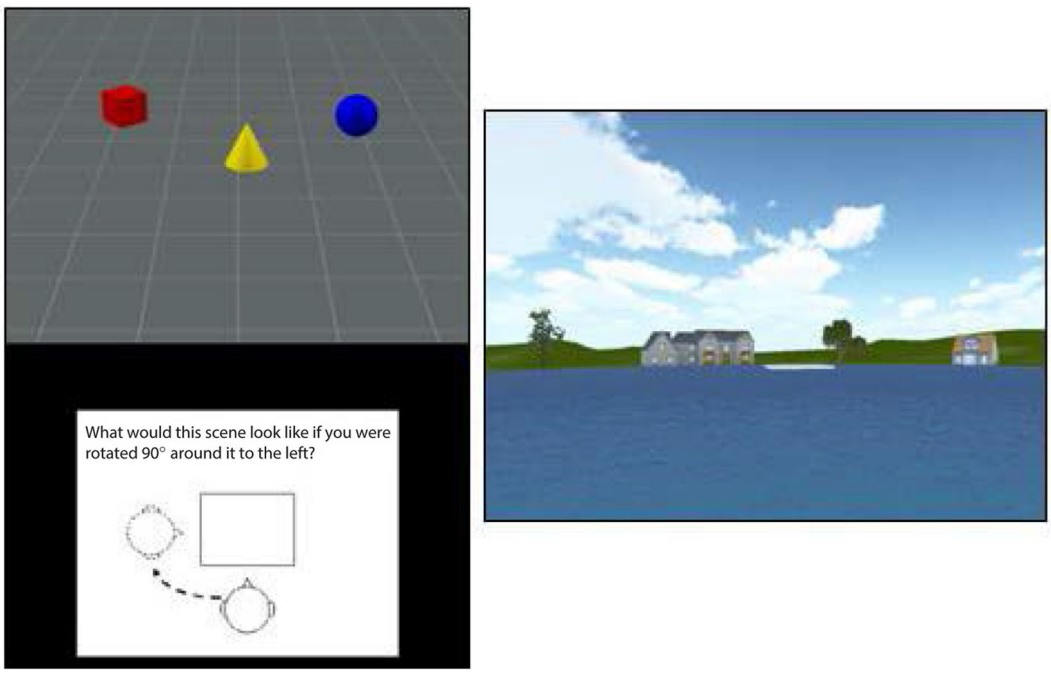


FIGURE 1 | An illustration of the stimuli used in the TMRT task (left) and pond maze (right). The figure at right shows the view from one of the six starting points in the pond task, with the platform shown in white in the center the pond image. The platform was visible on one-third of trials while it had to be reached from memory on the other two-thirds of trials.

Also, because time taken to reach the platform on the visible trials showed little variation among participants, presumably because forward speed was set by the software, only time to reach the platform on the nonvisible trials was used to assess navigational memory.

Visual pursuit

In the VP task, participants were required to follow a small red square as it moved from left to right. They were instructed to not move their head, and the experimenter additionally held the head in place from behind to prevent it from moving. The small red square had a diameter of 0.5° and moved from 21.8° left to 21.8° right at increasing sinusoidal velocities (0.1–0.4 Hz). Pursuit gain relative to the movement of the square was recorded at the highest frequency (0.4 Hz) and averaged across the left and right eyes.

Optokinetic nystagmus

In the OKN task, participants were required to gaze at an imaginary fixation spot in the center of the screen as columns of dots swept past at a velocity of 30°/s, first leftward then rightward. Each dot was 3.96° in diameter and each column was comprised of five dots spanning 37° vertically, with an inter-column distance of 13.34°. Participants were instructed to count the number of times a dot column crossed his or her imaginary fixation spot during a 30-s interval. They were also instructed to not move their head, with the experimenter again holding the head in place from behind to help prevent it from moving. The gain of the slow phase of the OKN relative to the movement of the dots was averaged across both eyes and both directions of dot-field motion.

Vestibulo-ocular reflex

The VOR was measured while participants fixated on the same red square as in the VP task, which remained stationary in the center of the visual field. They actively generated left-right head movements to the sound of a metronome at frequencies beginning at 1 Hz and increasing to 3 Hz (i.e., within the natural range of head movements). Only data when the head was moving at the proper frequency were used for analysis. Because it took some delay for the participant to begin synchronizing the head autorotations to the starting frequency of 1 Hz and because many participants could not easily generate the proper head motions at 3 Hz, only the VOR gains at 2 Hz were used in the final analysis. VOR gain was averaged across two trials and both eyes. Phase of the VOR was also recorded, but it was not analyzed because the reliability was very low (see Results section).

Postural control

Postural tests were conducted using the Equitest's Sensory Orientation Test (see http://resourcesonbalance.com/neurocom/products/EquiTest.aspx). The SOT provides an "equilibrium score" based on variations in the center-of-pressure under six different postural conditions in which the visual surround is either fixed or moves with the person's postural axis (sway-referenced) or the platform is fixed or moves with the person (sway-referenced). The six conditions involve: (1) visual scene and platform both fixed; (2) eyes-closed with platform fixed; (3) sway-referenced visual scene with platform fixed; (4) visual scene fixed with sway-referenced platform; (5) eyes-closed with sway-referenced platform; (6) sway-referenced visual scene with sway-referenced platform. Equilibrium scores were recorded for two trials in each condition, usually the first and second trials. Occasionally a third trial was run if the participant was outside of normal levels or suffered a fall on the first trial, which was almost entirely restricted to conditions 5 and 6. During each condition, participants were situated in a safety harness while their feet were evenly spaced from the center point and facing forward. Condition 1 is considered the baseline condition (normal standing), whereas Condition 5 relies on vestibular inputs given that visual and somatosensory inputs (the other two major sensory inputs to the postural control system) are eliminated due to the fact that the eyes are closed and the platform moves with the participant's postural sway (Black et al., 1995). Vestibular function was assessed in the standard manner by calculating the ratio of postural sway in Condition 5 to Condition 1.

Rotational memory

In this task, participants were seated in a barber chair that was locked and secured to the rotating turntable underneath. Participants were blindfolded and deprived of auditory inputs by means of ear plugs and ear muffs, which required a reliance on vestibular and, to a lesser extent, somatosensory cues. Participants received a sequence of nine trials in which they were rotated from the same starting point. Four of these trials involved single left or right rotations (to +/−30° or +/−40°), four involved combinations of eight left-right rotations (again ending at +/−30° or +/−40°), while the middle trial consisted of eight left-right rotations but ended up at the original starting position and served to disguise the pattern of the other eight end-positions. The five combination trials alternated with the single-rotation trials in a fixed order, with the control trial always being the fifth of nine. The nine trials consisted of the following sequences of rotations, in degrees: 1) 40R,20L,30R,20L,10R,40L,40R,30L,40R,20L (net = 30R); 2) 40L; 3) 20L,50R,20L,40R,30L,30R,40L,20R,30L,40R (net = 40R); 4) 30R; 5) 30L,50R,20L,10R,40L,10R,20L,30R,20L,30R (net = 0); 6) 30L; 7) 20R,50L,20R,40L, 30R,30L,40R,20L,30R,40L (net = 40L); 8) 40R; 9) 40L,20R,30L,20R,10L,40R,40L,30R, 40L,20R (net = 30L). On each trial, participants were instructed to point with arms outstretched to their perceived "straight-ahead" on the screen in front of them prior to the rotation, with the experimenter adjusting their arms to align the mark on the screen with the true straight-ahead. Immediately after the cessation of rotation, participants were instructed to aim the laser pointer to the spot on the screen where their original perceived straight-ahead intersected it, and the offset of the second mark from the first one reflected their rotational memory error, measured in degrees (RM°). After their laser pointer position was measured and recorded and their arms were relaxed, participants were then required to state whether they had ended up at or to the left or right of their original starting position (rotational direction memory (RM→). Participants were provided with some demonstrations and two practice trials to ensure they understood the task.

ANALYSIS

There were a total of 12 variables analyzed in this study. Six of them were independent variables related to vestibular or oculomotor function: VP, OKN, VOR, SOT, RM°, and RM→. Three additional demographic variables were included as covariates: age, education level (high school vs. college and above), and gender (male vs. female). The three topographical memory tasks (CTRMT, TMRT, and VPM) served as the dependent variables. In addition to descriptive statistics and bivariate correlations, backward stepwise multiple regressions were performed using SPSS software (IBM, Chicago, IL) for each topographical memory test, using the vestibular and demographic variables as predictors.

RESULTS

The means and standard deviations for the three topographical memory and six vestibular measures are shown in **Table 1**. The descriptive statistics showed a slightly less than perfect gain for the VP and optokinetic responses (0.83 and 0.88, respectively) and a slightly greater than unity gain (1.29) for the VOR, which involved actively generated head movements. On average, 1.6 of the direction judgments in the rotational memory task were incorrect, which is consistent with the fact that the mean rotational pointing error was 19.71° ($SD > 7°$) relative to the +/−30° and +/−40° endpoints. The most variable measures across participants were the TMRT and VPM and the SOT and RM°, where the standard deviation was a minimum of 30% of the mean. Part of the variability in the TMRT task was due to a very large difference between males ($M = 12.44$, $SD = 2.3$) and females ($M = 7.8$, $SD = 3.51$).

BIVARIATE CORRELATIONS

The bivariate correlation matrix involving the three topographical memory measures and six vestibular measures revealed only 2 of the 36 correlations to be statistically significant. The correlational analysis used the nonparametrc Spearman rank-order statistic, since a Shapiro-Wilk test showed significant violations of normality present for seven of the nine measures.

The highest correlations among the topographical memory measures themselves were between the TMRT and VPM scores ($\rho = -0.34$) and the CTRMT and VPM scores ($\rho = -0.37$), but both of these correlations were nonsignificant (The negative values indicate that as performance increased on the memory tasks, time taken to reach the platform in the maze task decreased).

Table 1 | Means and Standard Deviations for the topographical and vestibular measures.

Variable	*M*	*SD*
Camden Topographical Recognition Memory Test (correct out of 30)	24.44	4.3
Topographical Mental Rotation Test (correct out of 15)	9.52	3.74
Virtual Pond Maze (seconds)	34.2	11.0
Visual Pursuit (gain)	0.83	0.06
Optokinetic Nystagmus (gain)	0.88	0.15
Vestibular-Ocular Reflex (gain)	1.29	0.17
Sensory Orientation Test (ratio of conditions 5 to 1)	0.50	0.21
Rotational memory (° error)	19.71	7.43
Rotational memory (# correct out of 8 trials)	6.4	1.41

The correlations among the "vestibular" measures were almost entirely nonsignificant, with only the measures most directly assessing horizontal semicircular canal performance (VOR, RM°, and RM→) significantly correlated with each other ($\rho = -0.56$, $p < 0.01$ for RM→/RM° and $\rho = 0.53$, $p < 0.01$ for RM°/VOR). The significant negative correlation between VOR gain and degrees of rotational memory indicates that higher VOR gains were associated with poorer rotational memory performance. The correlations among the vestibular measures and between the vestibular and topographical measures suffered partly because the reliabilities of the vestibular measures themselves were not very high. For those measures where multiple trials were gathered, the reliabilities from one trial to the next (for the VOR and SOT measures) or from the first four trials to the second set of four (for the RM° and RM→ measures) ranged from 0.26 and 0.43 for the RM→ and RM° measures, respectively, to 0.49 and 0.62 for the VOR gain and SOT measures, respectively. It is impressive, therefore, that some of the *inter-vestibular* measures attained correlation coefficients in the range of the reliability of the individual measures themselves (>0.5).

Finally, there were only two correlations out of 18 between the vestibular measures and the topographical memory measures that exceeded 0.3 ($\rho = 36$ for RM→/TMRT and $\rho = -0.34$ for RM→/VPM); both of these were nonsignificant, however.

MULTIPLE REGRESSIONS

The regression models for the TMRT and VPM measures are listed in **Tables 2A** and **2B**. The regression model for the CTMRT measure was excluded because, despite an R value of 0.575, it did not prove statistically significant. For the TMRT measure, the significant regression model with the largest number of predictor variables included RM→, gender, VP, SOT, OKN, RM°, education level, VOR, and age. The combined R was 0.78 ($R^2 = 0.608$), while the largest adjusted R^2 (which takes into account the number of variables and sample size) was for the combination of RM→ and gender ($R^2 = 0.504$). The significant regression was based mainly on the fact that poorer rotational memory performance was associated with poorer TMRT scores; gender contributed as well because the TMRT means were so different between men and women. For the VPM measure, the model with the largest number of predictor variables included RM→, SOT, RM°, education level, and VOR. The combined R was 0.661 ($R^2 = 0.437$), while the largest adjusted R^2 was 0.289, for those same five predictors. The regression was based on the negative relationships of RM→, RM°, SOT, and educational level with the time to reach the platform and the positive relationship of VOR gain with time to reach the platform (the latter indicating that higher VOR gains were associated with poorer VPM performance).

DISCUSSION

The results of this study reveal that there is a linkage between vestibular function and topographical memory in a normal elderly human population. Because this was a correlational study,

Table 2A | Regression analysis for the Topographical Mental Rotation Test.

Variables	*R*	R^2	*Adj.* R^2	*df*	*F*	*P*
RM→; Gender; VP;SOT;OKN;RM°;Edu;VOR;Age	0.780	0.608	0.373	9,15	2.59	0.039
RM→; Gender; VP; SOT;OKN; RM°;Edu;Age	0.780	0.608	0.412	8,16	3.1	0.026
RM→; Gender; VP; SOT; RM°; Edu; Age	0.779	0.607	0.445	7,17	3.75	0.012
RM→; Gender; VP; SOT; RM°; Age	0.778	0.605	0.473	6,18	4.59	0.005
RM→; Gender; SOT; RM°; Age	0.762	0.580	0.469	5,19	5.25	0.003
RM→; Gender; RM°; SOT	0.754	0.568	0.481	4,20	6.52	0.002
RM→; Gender, RM°	0.730	0.532	0.465	3,21	7.97	0.001
RM→; Gender	0.710	0.504	0.459	2,22	11.17	0.000

Table 2B | Regression analysis for the Virtual Pond Maze.

Variables	*R*	R^2	*Adj.* R^2	*df*	*F*	*P*
RM→; RM°; VOR, SOT, Edu	0.661	0.437	0.289	5,19	2.95	0.039
RM→; RM°; VOR, SOT	0.628	0.394	0.273	4,20	3.26	0.033
RM→; RM°; VOR	0.557	0.310	0.212	3,21	3.15	0.046
RM→; RM°	0.503	0.253	0.185	2,22	3.73	0.04
RM→	0.404	0.164	0.127	1,23	4.50	0.045

no causal inference can be made about the vestibular role in topographical memory on the basis of these results alone. However, previous evidence from animal and human clinical studies does suggest a causal contribution of vestibular function to topographical memory.

The bivariate correlation matrix revealed modest but non-significant relationships among the three topographical measures and much stronger relationships among the three measures most directly linked to horizontal semicircular canal function (VOR, RM°, RM→). It is somewhat surprising that the correlations among the three topographical memory measures were not stronger, given that all have been linked to hippocampal/parahippocampal processing. However, it is possible that they tap into different aspects of the topographical memory process. For instance, only the TMRT measure showed a large difference between males and females, as found in other mental rotation tasks (Nazareth et al., 2013) involving the inferior parietal lobe. Also, the Camden topographical memory test involves less active mental transformations than do the pond maze and topographical mental rotation tasks.

It was not surprising that the correlation between the two rotational memory measures was significant, in that the measure of rotational direction occurred after the participant had made his or her mark with the laser pointer to indicate the original starting direction. The high correlation of rotational direction accuracy with VOR gain was more impressive in that it was about the same as the individual reliabilities for the two measures. It is noteworthy that the correlation between VOR gain and rotational accuracy was negative, with higher gains associated with lower accuracy. Unlike the passively generated VOR, actively generated VORs by means of head autorotation tend to have above-unity gains (Hirvonen et al., 1997), and it may be speculated that higher active VOR gains provided by corollary discharge boost performance in those individuals with diminished canal function. It is unlikely that the higher gains in individuals with poorer overall vestibular function were caused by a difference in the amplitude of the head autorotations, since preliminary measurements indicated that the size of the head movement did not affect actively generated VOR gain.

The relationship between the various measures of vestibular function and the topographical memory measures was more complex. On the one hand, no vestibular measures correlated significantly with any of the topographical memory measures. On the other hand, the significant regression models incorporating the greatest number of vestibular and oculomotor predictors and adjusted for gender, age, and education accounted for over 60% of the variance for the TMRT test and over 40% of the variance for the VPM measure. As previously noted, it is likely that the regression predictions would have been even better had they not been limited by the reliability of the vestibular measures themselves. On the other hand, there is a danger in incorporating a large number of variables with a relatively small sample size of 25, although even the adjusted R^2, which takes into account number of variables and sample size, proved impressive for the TMRT measure. It should be noted that the three measures of horizontal semicircular canal function tended to have slightly better predictive power in the regression analyses than did the SOT measure of vestibularly mediated postural control. This is consistent with the fact that the major vestibular inputs to the hippocampus emanate from the semicircular canals, signaling head rotation in the place of the Earth's surface (Taube et al., 1996; Previc, 2013).

A large number of human and animal studies have linked the vestibular system and hippocampus (Ossenkopp and Hargreaves, 1993; Horii et al., 1994; Sharp et al., 1995; Vitte et al., 1996; Taube et al., 1996; Brandt et al., 2005; Russell et al., 2006; Tai et al., 2012) as well as the vestibular system and topographical memory and other functions subserved by the hippocampus (Taube et al., 1996; Vitte et al., 1996; Brandt et al., 2005). The results of this study demonstrate that vestibular function and topographic memory are clearly related, but it is not clear

why. In contrast to evidence that vestibular damage induces behavioral, neuroanatomical, and neurophysiological alterations in the topographical memory system (Ossenkopp and Hargreaves, 1993; Brandt et al., 2005), it has never been shown that hippocampal or neocortical damage seriously disturbs vestibular function; hence, it is more likely that the causal direction flows from the vestibualar system. Because, however, both the vestibular system and the topographical memory system can be affected by general physiological deterioration (e.g., cardiovascular decline, diabetes, traumatic brain injury) (see Previc, 2013), it is also possible that the vestibular-topographical relationship can be explained by an outside factor affecting each separately.

The clinical implications for estimating any vestibular contribution to dementia of the Alzheimer's type (see Previc, 2013) are also unclear. As noted in the Introduction, topographical memory impairment, whether or not caused by vestibular dysfunction, is one of the earliest signs of Alzheimer's disease (Huang et al., 2002; Johnson et al., 2005; Berti et al., 2010; Pengas et al., 2012; Lithfous et al., 2013). By design, none of the participants in this study tested positive for dementia, but several of them showed clear impairments in topographical memory and may be at risk for developing more severe cognitive decline in the future. It cannot presently be ascertained whether a topographical memory and/or vestibular/oculomotor model could be used with diagnostic accuracy to predict who might later develop Alzheimer's. If, however, assessment of vestibular function can at least help identify those individuals at elevated risk for developing Alzheimer's, vestibular therapy, general exercise, and perhaps other vestibular interventions may serve as preventive measures to stave off the later cognitive decline (see Previc, 2013).

Unfortunately, it has been difficult to test Alzheimer's patients for vestibular performance. It can be a challenge to test even many normal elderly participants because of difficulties in moving their hips, knees and neck, keeping their eyelids from obscuring the view of the eye, and a host of other problems. That makes the rotational direction measure even more potentially valuable in this regard. It was the vestibular measure best correlated with the topographic memory measures and also the easiest to administer in that it did not involve any motor response on the part of the participant. This measure should be considered as a standard part of any otolaryngological assessment in the elderly population.

In summary, this study involving normal elderly participants has confirmed previous findings from the animal and human clinical literatures that a relationship between vestibular function and hippocampally mediated topographical memory exists. Future studies are required to better understand this relationship in both normals and those at greatest risk for Alzheimer's disease.

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From ear to uncertainty: vestibular contributions to cognitive function

Paul F. Smith* and Yiwen Zheng

Department Pharmacology and Toxicology, School of Medical Sciences, and the Brain Health Research Centre, University of Otago, Dunedin, New Zealand

Edited by:
Stephane Besnard, INSERM U1075, France

Reviewed by:
Alberto E. Pereda, Albert Einstein College of Medicine of Yeshiva University, USA
Stephane Besnard, INSERM U1075, France

****Correspondence:***
Paul F. Smith, Department Pharmacology and Toxicology, School of Medical Sciences, and the Brain Health Research Centre, University of Otago, Frederick St., 9045, Dunedin, New Zealand
e-mail: paul.smith@stonebow.otago.ac.nz

In addition to the deficits in the vestibulo-ocular and vestibulo-spinal reflexes that occur following vestibular dysfunction, there is substantial evidence that vestibular loss also causes cognitive disorders, some of which may be due to the reflexive deficits and some of which are related to the role that ascending vestibular pathways to the limbic system and neocortex play in spatial orientation. In this review we summarize the evidence that vestibular loss causes cognitive disorders, especially spatial memory deficits, in animals and humans and critically evaluate the evidence that these deficits are not due to hearing loss, problems with motor control, oscillopsia or anxiety and depression. We review the evidence that vestibular lesions affect head direction and place cells as well as the emerging evidence that artificial activation of the vestibular system, using galvanic vestibular stimulation (GVS), can modulate cognitive function.

Keywords: vestibular, spatial memory, cognition, hippocampus, vestibular lesions

INTRODUCTION

Recent epidemiological studies have demonstrated that vestibular disorders occur in more than 35% of adults aged 40 or older; between the ages of 60 and 69, the prevalence increases to almost 50% and between 70 and 79, it is 69% (Agrawal et al., 2009). Saber Tehrani et al. (2013) has estimated that, of 3.9 million patients visiting a Hospital Emergency Department for dizziness or vertigo in the USA in 2011, 25.7% were attributable to otological or vestibular causes, costing US $757 million. Vestibular dysfunction therefore represents a substantial and increasing burden on healthcare systems.

The most obvious effects of poor vestibular function are oscillopsia and ataxia (see Curthoys and Halmagyi, 1995 for a review); however, vestibular dysfunction involves a more complex syndrome characterized not only by reflex deficits, but also by attention and memory deficits, and anxiety disorders (see Smith et al., 2010 for reviews). It is evident that, in addition to the role of the vestibular system in the vestibulo-ocular and vestibulo-spinal reflexes (VORs and VSRs), the vestibular information provided in the ascending pathways to the limbic system and neocortex is required for an accurate internal representation of the relationship between the self and the spatial environment (Angelaki et al., 2009; chen et al., 2013). In the absence of this information, this internal representation becomes inaccurate, ambiguous, and cognitive performance is affected. The aim of this review is to summarize and critically evaluate the current literature relating to the effects of vestibular function on cognition.

ANIMAL STUDIES OF THE EFFECTS OF VESTIBULAR LESIONS ON MEMORY

Many of the early animal studies of spatial navigation suggested that non-visual, idiothetic cues such as vestibular and proprioceptive information, along with external, allocentric cues, were used by animals in order to remember how to navigate their way through a familiar environment (Beritoff, 1965; Potegal et al., 1977; Etienne, 1980; Mittelstaedt and Mittelstaedt, 1980; Horn et al., 1981; Potegal, 1982; Miller et al., 1983; Etienne and Jeffery, 2004). It was speculated that vestibular information must be transmitted to the hippocampus, in order to be integrated with other sensory information relevant to spatial memory (Wiener and Berthoz, 1993; Berthoz, 1996; McNaughton et al., 1996; Etienne and Jeffery, 2004). Ultimately it was reported that place cells in the hippocampus, that respond to specific places in the environment, were modulated by vestibular stimulation (Gavrilov et al., 1995; Wiener et al., 1995), which was supported by numerous animal behavioral studies showing that the disruption of normal vestibular function resulted in spatial memory deficits (Potegal et al., 1977; Horn et al., 1981; Potegal, 1982; Miller et al., 1983; Petrosini, 1984; Mathews et al., 1988, 1989; Semenov and Bures, 1989; Chapuis et al., 1992; Ossenkopp and Hargreaves, 1993; Stackman and Herbert, 2002; Wallace et al., 2002; Russell et al., 2003a; Zheng et al., 2003, 2006, 2007, 2008, 2009a,b, 2012a,b; Baek et al., 2010; Besnard et al., 2012; Machado et al., 2012a,b; Smith et al., 2013).

The early studies were open to the interpretation that what appeared to be spatial memory impairment following vestibular damage might be a direct result of oscillopsia, due to VOR deficits, or ataxia, due to VSR deficits. Such deficits never completely compensate even following a unilateral vestibular lesion (Smith and Curthoys, 1989; Curthoys and Halmagyi, 1995); therefore, this was a reasonable possibility. The first sophisticated study of spatial memory following bilateral vestibular lesions was reported by Wallace et al. (2002), who employed a foraging task, in which rats had to remember their way back to a home base, at 2

weeks post-op. This study, which used chemical lesions of the vestibular labyrinth with intratympanic sodium arsanilate, was well-controlled and used an electronic tracking system to quantify the rats' behavior. They found that rats with bilateral vestibular deaffferentation (BVD) exhibited profound spatial memory deficits in darkness, when visual cues were not available. Over the last decade in particular, many such studies have been conducted at much longer points after the lesion. Some compensation for the vestibular reflex deficits has occurred in the intervening period and yet the spatial memory deficits still persist (Zheng et al., 2006, 2007, 2008, 2009a,b, 2012a,b; Baek et al., 2010). In the study by Baek et al. (2010), which employed the longest post-operative time interval to date, rats that were 14 months post-BVD were more severely impaired in a spatial memory foraging task in darkness than at 5 months post-op. (see **Figures 1**, **2**).

EFFECTS OF UVD vs. BVD IN A SPATIAL MEMORY TASK IN DARKNESS

Especially important is that the spatial memory deficits exhibited by BVD rats were substantially more severe than for animals with unilateral vestibular deafferentation (UVD) (Zheng et al., 2006, 2009b). Rats with UVD showed spatial memory deficits in darkness at 3 months following the lesion, but performed at levels similar to sham controls at 6 months post-op. (Zheng et al., 2006). However, at 5–6 months post-op., while BVD rats had only minimally impaired performance in a foraging task in light, their performance deteriorated substantially in darkness (Zheng et al., 2009b). By 14 months post-op., rats with the same kind of BVD lesions were severely impaired in darkness (Baek et al., 2010; see **Figures 1**, **2**). In this latter study, even treatment with a cannabinoid receptor agonist, which would normally be expected to cause spatial memory impairment, could not increase the severity of the spatial memory deficits (**Figure 2**). These deficits in darkness suggest that oscillopsia is not necessary for the spatial navigation impairment to occur.

SPATIAL MEMORY DEFICITS IN LIGHT FOR BVD RATS

BVD rats have also been demonstrated to exhibit spatial memory deficits in light. At 6 weeks post-op., rats with BVD performed significantly worse than sham controls in a radial arm maze task even in light (Russell et al., 2003a,b). During spatial alternation in a T maze task in light, rats with BVD exhibited some improvement in performance over time, but at 5 months post-op. their percentage of correct responses was still significantly below normal (Zheng et al., 2007). This result was recently replicated by Zheng et al. (2012a,b), using rats at 4–5 months following BVD (see **Figure 3**).

Besnard et al. (2012) and Machado et al. (2012a,b) have recently demonstrated similar spatial memory deficits in light using the radial arm maze and Y maze in rats that had sequential unilateral chemical labyrinthectomies using sodium arsanilate (**Figure 4**). In an automated 5 choice serial reaction time task (5-CSRTT), which is a task commonly used to assess attentional performance in light, rats with BVD made significantly fewer correct responses, significantly more incorrect responses, with no more omissions, and responded with a reduced latency, compared to sham controls (Zheng et al., 2009a,b; see **Figure 5**). This study

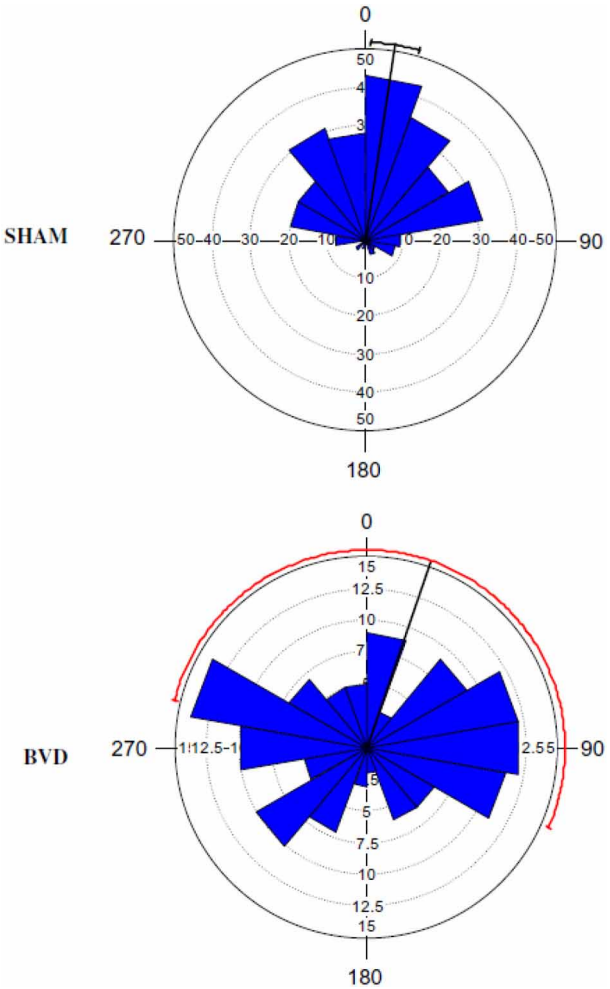


FIGURE 1 | A Rose diagram indicating the initial heading angles of SHAM and BVD rats at 14 months post-op. in a foraging task in darkness, in which they had to remember their way to a home base. The mean vector is indicated by the black line and the 95% confidence interval (CI) for the mean is indicated by the line extending either side. The 95% CIs for the BVD animals were unreliable due to the low concentration of vectors. The inner circles (dotted line) indicate the number of observations for the given vectors (blue triangles). Reproduced with permission from Baek et al. (2010).

in particular shows that the deficits of BVD rats in these cognitive tasks is not due to an inability to respond, but to incorrect responses.

These studies demonstrate that bilateral vestibular lesions have different effects in different cognitive tasks (i.e., radial arm maze, foraging task, Y and T mazes and 5-CSRTT) and that poor performance is not necessarily contingent upon the animal being in darkness, or light, where the oscillopsia would be expected to be worse, or due to an inability to respond. Therefore, the deficits are more likely to be due to an interaction between reduced cognitive ability and altered sensory input than altered sensory input alone. Studies over the last few years have aimed at elucidating the extent to which the spatial memory deficits may be due to other

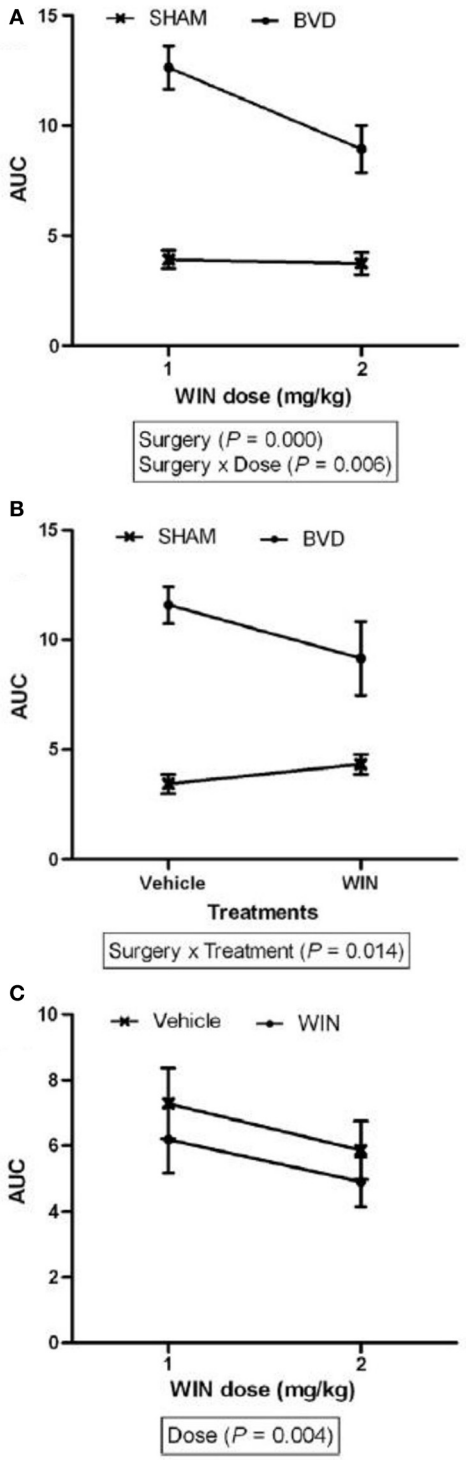


FIGURE 2 | The area under the curve (AUC) for the number of errors exhibited in the same foraging task described in Figure 1, for the sham and BVD animals at 14 month post-op. in darkness, showing the effects of surgery, drug treatment with a cannabinoid receptor agonist, WIN55,212-2 (which one would normally expect to make spatial memory worse), and their interaction. (A) Effects of surgery; **(B)** Drug treatment; and **(C)** Drug dose. Data are represented as mean ± s.e.m. Reproduced with permission from Baek et al. (2010).

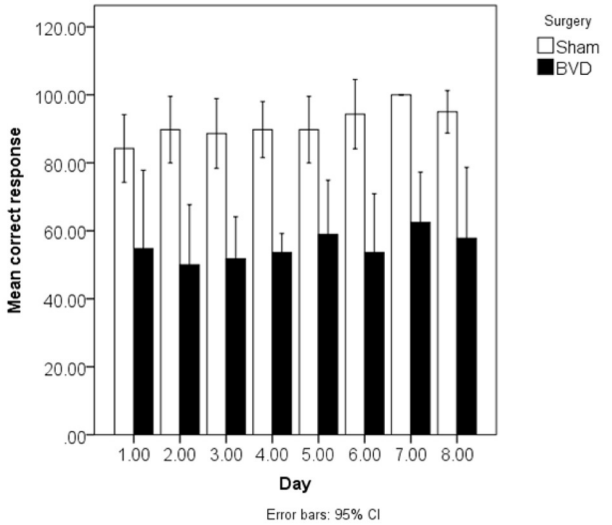


FIGURE 3 | Mean % correct responses in the spatial T maze task in light over 8 days for the BVD and sham animals at 4–5 months post-op. Reproduced with permission from Zheng et al. (2012a,b). Data are expressed as means ± a 95% confidence interval.

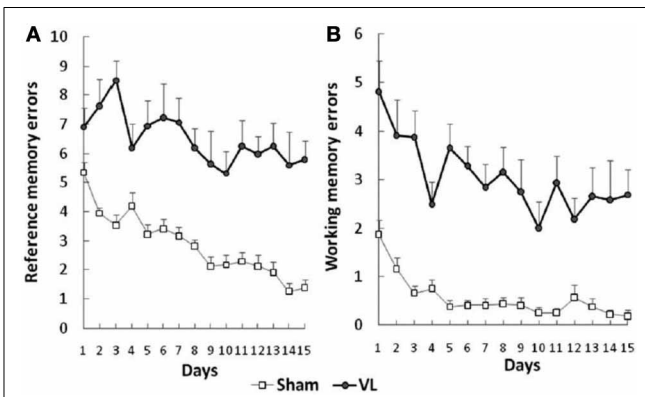


FIGURE 4 | Effects of sequential unilateral vestibular lesions on performance of rats, compared to sham controls, in a radial arm maze task. (A) Number of reference memory errors. **(B)** Number of working memory errors. Data are represented as mean ± s.e.m. Reproduced with permission from Besnard et al. (2012).

complications of BVD, such as changes in locomotor activity and anxiety.

POSSIBLE RELATIONSHIP BETWEEN SPATIAL MEMORY DEFICITS AND LOCOMOTOR HYPERACTIVITY

Most studies of rats with BVD indicate that they are hyperactive rather than hypoactive (Russell et al., 2003a,b; Goddard et al., 2008; Zheng et al., 2008, 2009a,b, 2012a,b; Baek et al., 2010; Besnard et al., 2012; Stiles et al., 2012; Machado et al., 2012b; see **Figure 6**). While this makes it difficult to explain poor performance in cognitive tasks in terms of an inability to move, it is conceivable that the hyperactivity prevents the animals from performing accurately in these various cognitive tasks. However,

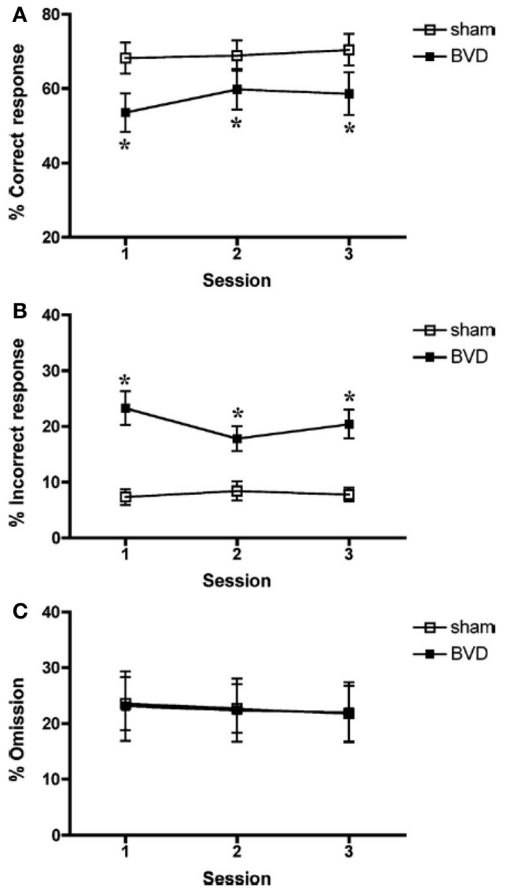


FIGURE 5 | Percentage of correct responses (A), incorrect responses (B), and omissions (C) for sham (open square) and BVD rats (closed square) in a 5 choice serial reaction time task in light. Data are expressed as means ± s.e.m. Asterisks indicate significant differences. Reproduced with permission from Zheng et al. (2009a,b).

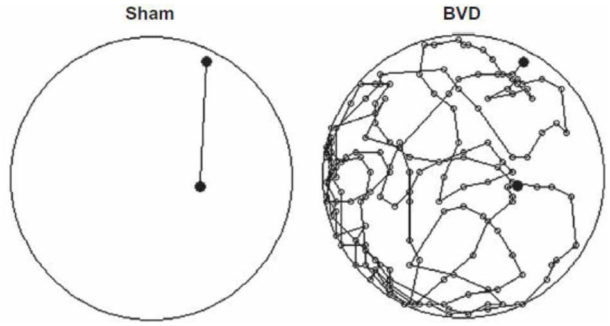


FIGURE 6 | An example of a homeward path taken by a BVD rat and a sham control rat at 14 months post-op. during a foraging task in darkness in which animals had been trained to forage for food and navigate their way back to a home base. Whereas the Sham rat traveled the shortest path back home, the BVD rat could not remember the correct path. Reproduced with permission from Baek et al. (2010).

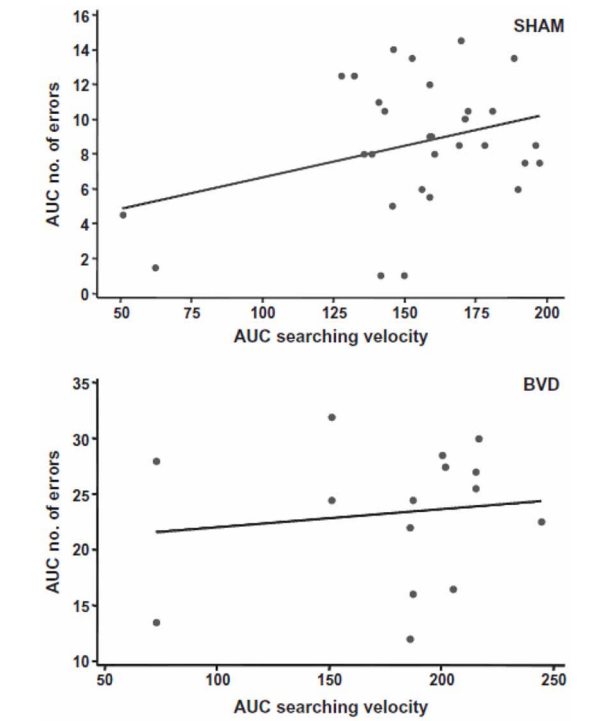


FIGURE 7 | A scatter graph showing a simple linear regression analysis to predict the number of errors made by all of the sham or BVD animals (in terms of the area under the curve) from their searching velocities in the foraging task, as an index of their locomotor hyperactivity. There was no significant prediction of spatial memory error from locomotor activity. Reproduced with permission from Baek et al. (2010).

Baek et al. (2010) used regression analyses to show that the poor performance of BVD rats in a foraging task could not be predicted by their hyperactivity (**Figure 7**). We have recently revisited this issue using multiple linear and random forest regression and found that hyperactivity cannot predict the poor performance of rats in a spatial T maze alternation task, but that the best predictors were whether the animals had received a BVD and the duration of their rearing in an open field maze (Smith et al., 2013; see **Figure 8**). These results suggest that the poor spatial memory performance of BVD rats cannot be explained by their locomotor hyperactivity. Further evidence in support of this conclusion is that even rats treated with diazepam and exhibiting anxiolytic behavior, still demonstrated the same spatial memory deficits in a radial arm maze task (Machado et al., 2012b).

POSSIBLE RELATIONSHIP BETWEEN SPATIAL MEMORY DEFICITS AND ANXIETY

It is possible that the association between vestibular dysfunction and anxiety and depression has some connection with the observed cognitive deficits that accompany vestibular lesions (Balaban and Thayer, 2001; Balaban, 2002; Staab and Ruckenstein, 2003; Staab, 2006). However, at least in animal studies, there is some evidence to disentangle anxiety and cognition in relation to BVD. Machado et al. (2012b) used the black and white box test to show that rats with BVD exhibited increased

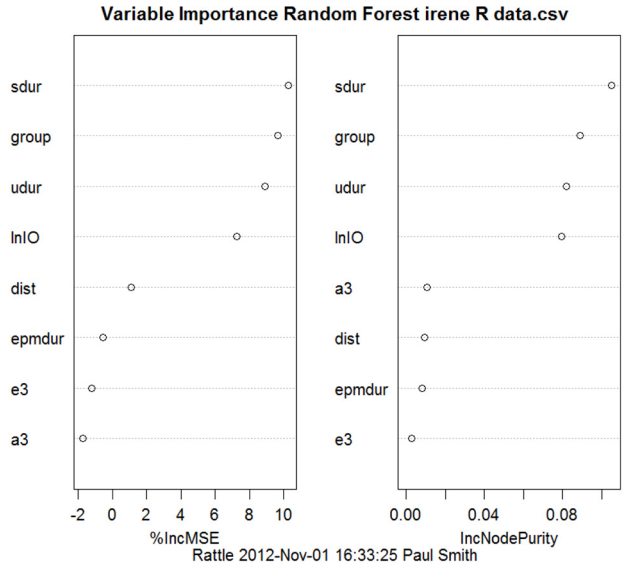


FIGURE 8 | Random forest regression, showing variables in order of importance from the top to the bottom, to predict the performance of BVD and sham animals in a spatial T maze task from the animals' performance in other behavioral tasks, such as the elevated plus maze, the open field maze and the elevated T maze. "group:" whether the animals had received a BVD or a sham operation. "epmdur:" duration of open arm entries in the elevated plus maze. "lnIO:" the ln of the ratio of time spent in the inner/middle to the outer zones of the open field maze. "e3:" 3rd escape latency in the elevated T maze. "a3:" 3rd avoidance latency in the elevated T maze. "dist:" distance traveled in the open field maze. "sdur:" duration of supported rearing in the open field maze. "udur:" duration of unsupported rearing in the open field maze. Reproduced with permission from Smith et al. (2013).

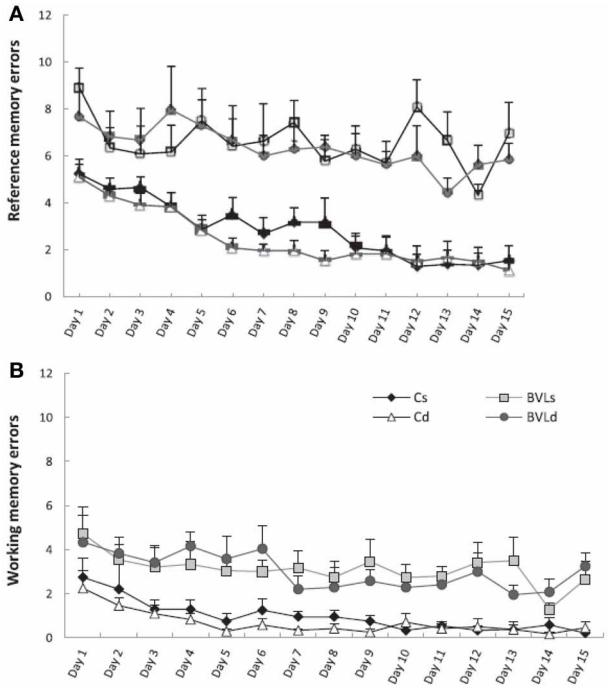


FIGURE 9 | Effects of 0.5 mg/kg diazepam, which was shown to have an anxiolytic effects, on spatial memory performance in a radial arm maze of bilateral vestibular lesion (BVL) and sham C rats. (A) Number of reference memory errors. **(B)** Number of working memory errors. Cs, control saline; Cd, control diazepam; BVLs, BVL saline; BVLd, BVL diazepam. Diazepam did not reduce the spatial memory deficits of the BVL rats. Data are expressed as means ± s.e.m. Reproduced with permission from Machado et al. (2012b).

anxiety and then administered diazepam to reduce it. Although the diazepam appeared to decrease the animals' anxiety, it had no effect on their poor performance in the radial eight-arm maze (**Figure 9**). Zheng et al. (2012a,b) attempted a similar experiment using the non-benzodiazepine anxiolytic drug, buspirone. In this case, the BVD animals did not exhibit increased anxiety in the elevated plus maze and buspirone had no effect on the time spent in the open arms of the maze, but neither did it have any effect on the animals' poor performance in a spatial forced alternation T maze task. Similarly, an anxiogenic drug, FG-7142, had no effect either on their spatial memory performance. Both of these studies suggest that, at least in animals, spatial memory deficits following BVD may be independent of anxiety.

VESTIBULAR vs. AUDITORY DAMAGE

One of the important limitations of the animal studies in this area is that chemical or surgical lesions of the vestibular labyrinth usually involve damage to the cochlea as well, and therefore it is possible that any cognitive effects of the lesions are partly due to hearing loss. For example, auditory stimulation, including noise trauma, has been reported to affect place cell function (Sakurai, 1990, 1994; Goble et al., 2009). For this reason, in most of our behavioral studies, sham control animals have their tympanic membranes removed so that sound is no longer transmitted effectively to the malleus, incus and stapes. This can serve as only a partial auditory control, however, because some sound will still be transmitted to the cochlea. Nonetheless, we have consistently found that rats without vestibular lesions but with the tympanic membrane removed perform significantly better in cognitive tasks than animals with vestibular lesions (Zheng et al., 2006, 2007, 2008, 2009a,b, 2012b; Baek et al., 2010). This result suggests that hearing loss is not the major cause of the spatial memory deficits in animals subjected to BVD, and is consistent with the results from studies of patients with vestibular dysfunction (e.g., Brandt et al., 2005). In addition, animal studies, using different kinds of aminoglycosides (i.e., streptomycin and neomycin) with different toxicities for the auditory and vestibular hair cells, have shown that the effects of auditory and vestibular lesions on learning and memory are different (Schaeppi et al., 1991). In a radial arm maze task, rats treated with streptomycin, which lesioned the auditory and the vestibular systems, exhibited impaired working memory; however, rats treated with neomycin, which lesioned only the auditory system, did not (Schaeppi et al., 1991). In our tinnitus studies we have found that a unilateral acoustic trauma has no significant effect on spatial memory (Zheng et al., 2011).

It is not clear whether the cognitive deficits associated with vestibular dysfunction in animals are limited to spatial memory impairment. Some animal studies using surgical BVD have also reported deficits in attention (Zheng et al., 2009a) and in object recognition memory that has no spatial component (Zheng et al., 2004). However, others using sequential chemical UVDs have reported no deficits in object recognition memory (Besnard et al., 2012); therefore, this issue remains to be resolved due to methodological differences between the existing studies.

HUMAN STUDIES OF THE VESTIBULAR LESIONS ON MEMORY

One of the first clinical studies of cognitive function following vestibular loss was reported by Grimm et al. (1989). They described patients with a perilymph fistula syndrome, who reported symptoms such as positional vertigo but also a variety of psychological symptoms, including memory and attention deficits. From a total of 102 patients, more than 85% of them reported memory loss. The patients had a normal level of intellectual function; however, their performance on digit symbol, block design, paired associate learning and picture arrangement tasks, was impaired. Following this, several studies in the 1990's examined the effects of vestibular damage on spatial navigation in humans. They showed that patients with vestibular disorders exhibited deficits in path navigation (Peruch et al., 1999; Cohen, 2000; Cohen and Kimball, 2002; Borel et al., 2004). However, the tasks involved movement, and therefore it could be argued that the deficits resulted from a complex interaction between cognition and postural control. Other studies examined cognitive performance more directly. Black et al. (2004) found that memory problems were common in patients with vestibular loss due to gentamicin ototoxicity. Jauregui-Renaud and colleagues have published a number of studies reporting that patients with vestibular disorders have high rates of depersonalization/derealization symptoms, which include difficulty focussing attention and thoughts seeming blurred (Sang et al., 2006; Jauregui-Renaud et al., 2008a,b; see Gurvich et al., 2013, for review). Other studies have shown that as postural tasks become more challenging, patients with vestibular disorders exhibit deficits in reaction time and memory (Yardley et al., 2001, 2002; Redfern et al., 2004). In a study by Redfern et al. (2004), patients with unilateral vestibular loss showed large increases in complex and inhibitory reaction time, even while seated. A similar result was reported by Talkowski et al. (2005).

BILATERAL vs. UNILATERAL VESTIBULAR LESIONS

The most sophisticated and well-controlled studies of spatial memory following vestibular lesions in humans, have been reported by Schautzer et al. (2003) and Brandt et al. (2005), who examined the performance in a spatial memory test, the virtual Morris water maze, of 10 patients with bilateral vestibular loss and compared them with age-, sex- and education-matched controls. The task involved moving only a cursor on a computer screen, using a mouse; therefore, performance in the spatial memory task could not have been confounded by VSR deficits. The patients had received bilateral vestibular neurectomies 5–10 years previously for the treatment of neurofibromatosis type 2. They found that the patients with bilateral vestibular loss showed impaired performance in the task when they had to remember a navigation path to a previously visible target; however, they showed no deficit when the target was visible, therefore the effect was specific to memory (see **Figure 10**). Brandt et al. used the Weschler memory test to show that the patients had normal or above normal non-spatial memory performance. Compared to the controls, the patients also exhibited a significant decrease in the volume of the hippocampus (16.9%). This effect was bilateral, specific to the hippocampus and there was no significant reduction in the total brain volume or in the volume of gray matter or white matter, only a significant increase in cerebrospinal fluid volume. Importantly, only one of the BVD patients had total post-operative hearing loss.

In a study of patients with UVD, Hüfner et al. (2007) reported results from the virtual Morris water maze task that were more complex. During place learning, males with a right UVD and females with a left UVD exhibited a significantly smaller decrease in heading error over the repeated trials compared to the controls and other UVD groups. In addition, inspection of the swim paths showed that only 2 out of the 8 right UVD patients used direct paths to the platform, compared to 12 out of the 16 control subjects, a difference that was statistically significant. In the probe trial, the right UVD patients were found to have a greater heading error than the left UVD patients or control subjects. Finally, in the cued navigation, females with a left UVD performed worse than the other groups in the first visible platform trial. By contrast with the study of Brandt et al. (2005) of patients with BVD, Hüfner et al. (2007) found no significant differences in the hippocampal volume of UVD patients compared to controls. In a later study, Hüfner et al. (2009) reported some subtle deficits in spatial memory in patients with UVD as well as an atrophy of the ipsilateral supramarginal nucleus, the postcentral and superior temporal gyrus and the MT/V5 area, as well as the contralateral thalamus and tegmentum of the mesencephalon. However, zu Eulenburg et al. (2010) reported that patients who

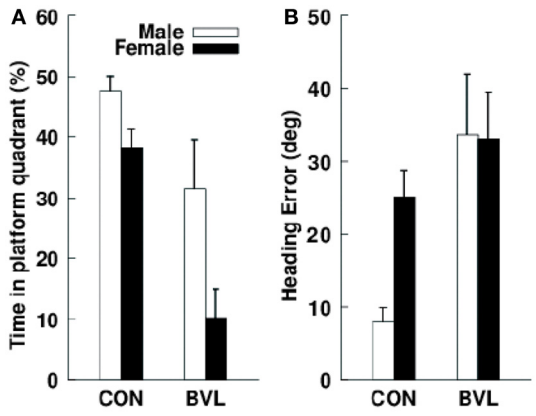


FIGURE 10 | (A) Mean percentage search time that male and female control and bilateral vestibular lesion (BVL) patients spent in the correct platform quadrant during the no-platform trial in a virtual Morris water maze task. **(B)** Initial heading error in the same task. Data are expressed as means ± s.e.m. Reproduced with permission from Brandt et al. (2005).

had recovered from unilateral vestibular neuritis, exhibited a significant decrease in the volume of the left posterior hippocampus, irrespective of the laterality of the vestibular neuritis. Helmchen et al. (2013) have recently reported the results of a resting state fMRI study of patients with vestibular neuritis. They identified a network of brain regions that was significantly different from controls, including the parietal lobe, the medial aspect of the superior parietal lobule, the posterior cingulate cortex, the middle frontal gyrus, the middle temporal gyrus, the parahippocampal gyrus, the anterior cingulate cortex, the insular cortex, the caudate nucleus, the thalamus and the midbrain.

Consistent with these studies, Hüfner et al. (2010) reported structural changes in the hippocampi of professional dancers and slackliners, who have unusual spatial memory experience. Hufner et al. found that trained subjects exhibited a smaller anterior volume, and a larger posterior volume, in the hippocampal formation, although they showed no difference in spatial memory compared to controls, according to the virtual Morris water maze test.

It is apparent from these studies that the volume of the human hippocampus is sensitive to vestibular input. While the effects of BVD are the most dramatic (Brandt et al., 2005), the effects of unilateral vestibular loss are more circumscribed (Hüfner et al., 2007; zu Eulenburg et al., 2010; Helmchen et al., 2013).

Vestibular disorders have also been reported to impair mental imagery tasks that involve imagined rotations or translations of objects relative to the environment, which are also spatial in nature (Péruch et al., 2011). Grabherr et al. (2011) found that only patients with bilateral vestibular loss, and not unilateral vestibular loss, exhibited impaired ability to mentally transform images of bodies and body parts compared to controls.

It is not entirely clear whether the cognitive deficits associated with vestibular dysfunction in humans are limited to spatial memory impairment. While some studies have reported that other aspects of memory, attention and general intelligence are normal (Schautzer et al., 2003; Brandt et al., 2005), others have reported deficits in attention and concentration (Sang et al., 2006; Jauregui-Renaud et al., 2008a,b) and even dyscalculia (Risey and Briner, 1990-1991; Andersson et al., 2002, 2003; Yardley et al., 2002; see Smith, 2012 for a review).

POSSIBLE CONNECTION WITH VESTIBULAR REFLEX DYSFUNCTION AND VERTIGO

As with the animal studies, it is possible that any memory impairment following vestibular damage might simply be a result of vestibular reflex deficits, for example, the inability to see clearly due to oscillopsia or ataxia as a consequence of impaired VORs and VSRs (respectively) (Gizzi et al., 2003). However, studies such as those by Schautzer et al. (2003) and Brandt et al. (2005) were conducted 5–10 years following bilateral vestibular neurectomy. Although the patients would never have recovered normal VOR and VSR function, they would have compensated for the severe acute symptoms (Smith and Curthoys, 1989; Curthoys and Halmagyi, 1995).

Given the severity of some vestibular disorders such as Ménière's disease, it is possible that any cognitive dysfunction is an indirect consequence of symptoms such as vertigo. However, studies of patients with chronic vestibular loss without vertigo, have reported that the patients still exhibit spatial memory impairment (Guidetti et al., 2008). Overall, it seems that patients with at least bilateral vestibular loss, suffer from cognitive problems, particularly spatial memory impairment, that are not simply a direct result of vestibular reflex dysfunction (see Smith et al., 2005a,b; Hanes and McCollum, 2006; Smith et al., 2009, 2010; Gurvich et al., 2013, for reviews).

POSSIBLE CONNECTION WITH ANXIETY AND DEPRESSION

In the case of humans, it is much more difficult to separate poor performance in cognitive tests from emotional disorders. Vestibular dysfunction in humans is often associated with anxiety disorders, including panic attacks and phobias, as well as depression (Eagger et al., 1992; Asmundson et al., 1998; Balaban and Thayer, 2001; Balaban, 2002; Furman and Jacob, 2001; Monzani et al., 2001; Grunfeld et al., 2003; Persoons et al., 2003; Pollak et al., 2003; Godemann et al., 2004a,b, 2009; Best et al., 2006; Staab, 2006; see Gurvich et al., 2013, for review). Anxiety may be a direct consequence of vestibular dysfunction; however, it has also been reported that anxiety disorders can cause dizziness of vestibular origin (Asmundson et al., 1998; Venault et al., 2001; Bolmont et al., 2002; Staab et al., 2002; Tecer et al., 2004; Best et al., 2006; Furman et al., 2006) and antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported to relieve dizziness associated with anxiety (Staab et al., 2002; Simon et al., 2005; Horii et al., 2007). It possible that emotional disorders arise indirectly from cognitive impairment. However, Halberstadt and Balaban (2006) have reported that the same neurons in the dorsal raphe nucleus that release serotonin, send projections into the amygdala, as well as the brainstem vestibular nucleus. This finding suggests that changes in emotional tone may directly influence the vestibular system.

It is worth noting here that the hippocampus is as much an emotional brain region as one that contributes to spatial memory (Gray and McNaughton, 2003). While the rat dorsal hippocampus (approximately equivalent to the posterior hippocampus in humans) is involved in spatial information processing and spatial memory, the rat ventral hippocampus (approximately equivalent to the anterior hippocampus in humans) processes emotional stimuli (Bannerman et al., 1999, 2004). Therefore, it may be difficult to disentangle the effects of vestibular loss on cognition and emotion.

EFFECTS OF VESTIBULAR LESIONS ON HEAD DIRECTION CELL AND PLACE CELL FUNCTION

Taube and colleagues have shown that bilateral inactivation of the vestibular labyrinth, using intratympanic tetrodotoxin, results in the dysfunction of thalamic head direction cells (Stackman and Taube, 1997; see Brown et al., 2002 for a review). In other studies, they have shown that head direction cell activity is degraded during inverted locomotion (Calton and Taube, 2005) and as a result of the loss of vestibular information from either the otoliths (Yoder and Taube, 2009) or the semi-circular canals (Muir et al., 2009). Also using intratympanic tetrodotoxin, Stackman et al. (2002) first reported that loss of vestibular function resulted in a disruption of the selective firing of hippocampal place cells in

alert rats. One of the most important aspects of this result was that the disruption to place cell firing patterns was immediate, and it recovered over time, indicating that long-term changes in hippocampal structure were unnecessary for the changes in place cell function. This result was replicated by Russell et al. (2003b) using permanent surgical BVD in rats.

Hippocampal theta rhythm is a large amplitude, quasi-sinusoidal EEG rhythm of ∼5–12 Hz which is believed to serve a cohesive function for the firing of hippocampal place cells (Hasselmo, 2005; Vertes, 2005). Many studies in alert animals have reported that theta rhythm in the frequency range of 6–9 Hz can be recorded during movement (see Zou et al., 2009 for a review). In fact, theta frequency has been shown to increase with increasing speed of locomotion (Jeewajee et al., 2008; Lever et al., 2009). Very few studies have investigated the effects of vestibular lesions on theta rhythm. Stackman et al. (2002) investigated theta in one rat in a study in which they transiently inactivated the vestibular system. In the one animal in which they analyzed theta, they found no significant difference from control animals. Russell et al. (2006) used permanent surgical BVD to investigate the effects of vestibular loss on theta rhythm. In contrast to Stackman et al. (2002), they found that hippocampal theta rhythm was severely disrupted. Not only was the power of theta reduced following BVD, but the quasi-sinusoidal character of the waveform was corrupted. Although the BVD animals were hyperactive, theta rhythm was abnormal across the entire range of movement velocities. These results have recently been replicated by Neo et al. (2012), who tried but failed to reverse the spatial memory and emotional deficits caused by BVD by electrically stimulating the septum in order to provide an artificial theta rhythm. Tai et al. (2012) also recently showed that rats that are administered sodium arsanilate intratympanically exhibit a reduction in theta power.

Taken together, these animal studies support the view that vestibular information is important for the generation of spatial memories (Wiener and Berthoz, 1993; Berthoz, 1996; McNaughton et al., 1996, 2006; Etienne and Jeffery, 2004; Smith et al., 2005a,b, 2009, 2010). It is still unclear how vestibular information reaches the hippocampus. Electrical stimulation of one vestibular labyrinth or of the vestibular nucleus has been reported to evoke field potentials, single unit activity and neurotransmitter release in the hippocampus, albeit with a long latency (Horii et al., 1994, 2004; Cuthbert et al., 2000). Caloric or electrical stimulation of the human labyrinth has been shown to cause activation of the hippocampus (Vitte et al., 1996; De Waele et al., 2001) and glucose uptake is reduced in the hippocampus in patients with acute vestibular neuritis (Bense et al., 2001). The thalamus is certain to be one important relay station for the transmission of at least some ascending vestibular information. However, the number of different vestibulo-hippocampal pathways and their precise nature, remains to be determined (Smith, 1997; see Shinder and Taube, 2010 and Hufner et al., 2011 for recent reviews). It must also be kept in mind that the hippocampus is only one part of a highly complex system of limbic-neocortical pathways that are responsible for spatial memory (Guldin and Grusser, 1998; Hanes and McCollum, 2006; Gu et al., 2007; Shinder and Taube, 2010; Lopez and Blanke, 2011). In humans, fMRI has revealed that areas of significant activation by galvanic vestibular stimulation (GVS) include the posterior insula, the retroinsular regions, the superior temporal gyrus, parts of the inferior parietal lobule, the intraparietal sulcus, the post-central and pre-central gyrus, the anterior insular, the inferior frontal gyrus, the anterior cingulate gyrus, the precuneus and the hippocampus (Lobel et al., 1998; see Karnath and Dieterich, 2006 for a review). Activation of cortical networks during GVS is not symmetrical; it appears to be stronger in the non-dominant hemisphere, in the hemisphere ipsilateral to the stimulated ear, and in the hemisphere ipsilateral to the fast phase of vestibular nystagmus (see Karnath and Dieterich, 2006 for a review).

Despite the finding by Brandt et al. (2005) that patients with BVD exhibit a bilateral atrophy of the hippocampus, studies in BVD rats have so far failed to detect such a change. Using a sequential chemical BVD procedure, Besnard et al. (2012) found no significant change in hippocampal volume using MRI. Likewise, Zheng et al. (2012a) could find no change hippocampal volume or neuronal number using stereology. Nonetheless, in unpublished studies, we have found a significant decrease in dendritic length in the hippocampi of BVD rats. One possibility is that hippocampal volume is maintained in rats following BVD due to their locomotor hyperactivity, since movement is known to stimulate hippocampal neurogenesis. Interestingly, Zheng et al. (2012a) observed a significant increase in cell proliferation in the rat hippocampus following BVD. Besnard et al. (2012) also reported an increase in NMDA receptor density and a decrease in affinity in BVD rats. Although Zheng et al. (2013) did not find significant differences in glutamate receptor subunit expression in rats with BVD, principal component analysis did reveal subtle changes in the relationship between different NMDA receptor subunits (Smith and Zheng, 2013). Because Besnard et al. (2012) used autoradioradiography with beta imaging, their results may reflect functional NMDA receptors rather than the total receptor pool.

EFFECTS OF ARTIFICIAL VESTIBULAR ACTIVATION ON MEMORY IN HUMANS

A small literature exists on the use of low amplitude, noisy GVS to enhance cognition in humans. The overlaying of a noise signal on a galvanic stimulus, termed "noisy GVS," is based upon the concept of stochastic resonance, in which a sub-threshold sensory stimulus can be made to exceed a fixed threshold if a Gaussian noise signal, with a frequency much higher than the sub-threshold stimulus, is superimposed upon it (Moss et al., 2004).

Bächtold et al. (2001) was the first to report that caloric vestibular stimulation (CVS) could improve verbal and spatial memory in humans, and the effect was greater for right ear irrigation. However, CVS induces vestibular reflexes and therefore it is difficult to separate those effects from cognitive performance. Falconer and Mast (2012) have recently reported that CVS can enhance performance in an egocentric transformation task.

In a later study, Wilkinson et al. (2008) investigated whether noisy, low intensity, bipolar GVS, which was sub-threshold for the activation of the vestibular reflexes, could affect memory for faces. They found that the mean reaction time was shorter for the GVS

groups compared to the sham controls, but that the largest reduction was for the anode on the left ear and the cathode on the right ear. They concluded that GVS can improve memory for faces, perhaps by increasing blood flow to the right temporal and parietal cortices. This effect of GVS on memory was unlikely to be due to non-specific arousal since the electrical stimulation was subthreshold, the memory improvement was greater for the anode on the left, and improvement was found only when a noise signal was added to the GVS. Wilkinson and colleagues have also found that noisy GVS can attenuate prosopagnosia (Wilkinson et al., 2005) and figure copying deficits (Wilkinson et al., 2010). In the most recent study involving two patients with visuo-spatial neglect, GVS was found to have a lasting beneficial effect in a target cancellation task (Zubko et al., 2013). In one of the most systematic studies to date, Dilda et al. (2012) found that suprathreshold GVS significantly increased the error rates for match-to-sample and perspective-taking tasks compared to a subthreshold GVS group; however, reaction time, dual tasking, mental rotation and manual tracking were not significantly affected. Subthreshold GVS had no significant effect on cognitive performance compared to the pre-stimulus conditions.

At the present, there is very little evidence relating to how noisy GVS affects memory. It is not clear whether the effect has any relationship to the effects of vestibular lesions on spatial memory. One possibility is that any beneficial effect of GVS is merely a result of the fact that vestibular information reaches many regions of the neocortex (Bense et al., 2001) and that it will probably cause a change in the integration of sensory information (Wilkinson et al., 2008). However, given the importance of vestibular information to spatial memory, sub-threshold GVS may somehow "prime" the brain to process and store new information. Wilkinson et al. (2012) have recently reported that GVS increased the amplitude of the N170 potential and the power of delta and theta EEG during a face processing task. It is noteworthy that many of these effects of GVS are not restricted to spatial attention or memory. A more recent study by Kim et al. (2013) also supports the idea that GVS modulates neural oscillations.

CONCLUSIONS

Over the last 12 years in particular, a substantial body of evidence has accumulated to suggest that the loss of vestibular function results in cognitive disorders, especially spatial memory deficits that cannot easily be attributed to the direct effects of reflex dysfunction, motor control problems or hearing loss. The spatial memory deficits appear to be most striking in the case of BVD, where there is a complete loss of vestibular function, although there are many more animal studies than human studies to substantiate this. It will be particularly important in future studies to further investigate the effects of unilateral and bilateral vestibular loss in humans, on different types of cognitive function.

In animals at least, the spatial memory deficits appear to be independent of anxiety, although this is less conclusive in humans. One reason to be cautious about disentangling the effects of vestibular damage on cognition and emotion, is that the hippocampus is deeply involved in both (Gray and McNaughton, 2003). While lesions of the dorsal hippocampus in rats result in spatial memory deficits and locomotor hyperactivity, lesions of the ventral hippocampus result in reduced anxiety in the elevated plus maze and hyponeophagia (Bannerman et al., 2002). It is intriguing that BVD, in addition to causing spatial memory deficits and locomotor hyperactivity in rats, has been reported to cause both reduced anxiety in the elevated plus and T mazes (Zheng et al., 2008; Neo et al., 2012) and hyponeophagia (Zheng et al., 2008). This might suggest that BVD results in behavioral effects that are similar to both dorsal and ventral hippocampal lesions and that it may be very difficult to disentangle them completely.

The cognitive effects of vestibular loss appear to be due mainly to the important contribution that the vestibular system makes to neurons involved in spatial navigation and memory, such as head direction cells and place cells, although exactly how this information is used remains to be determined. Information from the otoliths as well as the semi-circular canals seems to be necessary for the normal function of head direction cells; however, so far the different contributions of the otoliths and semi-circular canals to hippocampal place cell function have not been investigated. Furthermore, despite the attention to the thalamus and hippocampus, many different areas of the limbic system and neocortex are involved in these spatial memory processes. Since grid cells in the entorhinal cortex are thought to be responsible for the place fields of hippocampal place cells (see Giocomo et al., 2011 for a review), it might be predicted that BVD would severely disrupt grid cell firing; however, this has not been investigated to date. Future studies will need to specifically address how vestibular information is transmitted to the dorsal and ventral hippocampus in rats and the extent to which otolithic vs. semi-circular canal input is represented in different areas of the hippocampus and entorhinal cortex. At present, we know that vestibular input is necessary for the normal function of the hippocampus but we do not understand how this input is being used.

At present there is some evidence that artificial activation of the vestibular system, using noisy GVS, can modulate memory. However, at present this literature is small and it is unclear whether this effect, when it occurs, is related to the same mechanisms by which vestibular lesions affect memory.

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Plasticity of the histamine H_3 receptors after acute vestibular lesion in the adult cat

***Brahim Tighilet*[1]*, *Christiane Mourre*[2] *and *Michel Lacour*[1]**

[1] *Laboratoire de Neurosciences Intégratives et Adaptatives, UMR 7260, FR - Comportement, Cerveau, Cognition (Behavior, Brain, and Cognition), Centre Saint-Charles, Case B, Centre National de la Recherche Scientifique, Aix-Marseille Université, Marseille, France*
[2] *Laboratoire de Neurosciences Cognitives, UMR 7291, Centre Saint-Charles, Centre National de la Recherche Scientifique, Aix-Marseille Université, Marseille, France*

Edited by:
Pierre Denise, Université de Caen Basse-Normandie, France

Reviewed by:
Catherine de Waele, Centre National de la Recherche Scientifique, France
Christian Chabbert, Institut National de la Santé et de la Recherche Médicale, France

***Correspondence:**
Brahim Tighilet, Laboratoire de Neurosciences Intégratives et Adaptatives, UMR 7260, FR - Comportement, Cerveau, Cognition (Behavior, Brain, and Cognition), Centre Saint-Charles, Case B, Centre National de la Recherche Scientifique, Aix-Marseille Université, 3 Place Victor Hugo, 13331 Marseille Cedex 03, France
e-mail: brahim.tighilet@univ-amu.fr

After unilateral vestibular neurectomy (UVN) many molecular and neurochemical mechanisms underlie the neurophysiological reorganizations occurring in the vestibular nuclei (VN) complex, as well as the behavioral recovery process. As a key regulator, the histaminergic system appears to be a likely candidate because drugs interfering with histamine (HA) neurotransmission facilitate behavioral recovery after vestibular lesion. This study aimed at analyzing the post-lesion changes of the histaminergic system by quantifying binding to histamine H_3 receptors (H_3R; mediating namely histamine autoinhibition) using a histamine H_3 receptor agonist ([^{3}H]N-α-methylhistamine). Experiments were done in brain sections of control cats ($N = 6$) and cats submitted to UVN and killed 1 ($N = 6$) or 3 ($N = 6$) weeks after the lesion. UVN induced a bilateral decrease in binding density of the agonist [^{3}H]N-α-methylhistamine to H_3R in the tuberomammillary nuclei (TMN) at 1 week post-lesion, with a predominant down-regulation in the ipsilateral TMN. The bilateral decrease remained at the 3 weeks survival time and became symmetric. Concerning brainstem structures, binding density in the VN, the prepositus hypoglossi, the subdivisions of the inferior olive decreased unilaterally on the ipsilateral side at 1 week and bilaterally 3 weeks after UVN. Similar changes were observed in the subdivisions of the solitary nucleus only 1 week after the lesion. These findings indicate vestibular lesion induces plasticity of the histamine H_3R, which could contribute to vestibular function recovery.

Keywords: histamine H_3 receptor, unilateral vestibular neurectomy, vestibular compensation, vestibular nuclei, tuberomammillary nuclei, inferior olive, solitary nucleus, cat

INTRODUCTION

Unilateral lesion of the peripheral vestibular system induces a syndrome of static oculomotor (nystagmus) and postural (head roll- and yaw-tilt, asymmetric extensor tone in the limb and axial muscles, increase of the surface delimited by the four legs) disorders that subside quite rapidly (few days or weeks) in a process of behavioral recovery known as vestibular compensation. This unilateral vestibular damage induces also dynamic symptoms such as vestibulo-ocular reflex gain deficit toward the lesioned side that are however long-lasting or remain relatively uncompensated. The neural mechanisms underlying this vestibular function recovery has been well documented and it is admitted that the static deficits result from the asymmetric resting discharge and their compensation is associated with a rebalanced resting activity on both sides. By contrast the compensation of the dynamics symptoms involves multiple plasticity mechanisms occurring in various brain areas (Smith and Curthoys, 1989; Curthoys, 2000; Dieringer, 2003; Lacour, 2006; Paterson et al., 2006; Dutia, 2010; Lacour and Tighilet, 2010).

Neuromodulators such as histamine could influence these plasticity mechanisms and may thus contribute to the vestibular recovery process. Numerous basic and pharmacological studies in intact and vestibular-lesioned animals, as well as in humans, put forward a link between brain histamine (HA), vestibular function and its recovery after vestibular damage. Indeed, the central histaminergic system is involved in the regulation of vestibular functions and their recovery after vestibular lesion (Bergquist and Dutia, 2006; Haas et al., 2008; Lacour and Tighilet, 2010). Histamine is highly implicated with the arousal level (Brown et al., 2001; Haas et al., 2008) and it has been shown that the horizontal vestibulo-ocular-reflex gain was very sensitive to the state of alertness (Flandrin et al., 1979; Matta and Enticott, 2004). Stimulation of the vestibular nerve enhances HA release in the hypothalamus and brainstem (Takeda et al., 1986; Horii et al., 1993, 1996; Uno et al., 1997). *In vitro* intracellular recordings from neurons in the medial and the lateral vestibular nuclei (VN; MVN and LVN) revealed HA induced depolarization via postsynaptic histamine H_1 (H_1R; Inverarity et al., 1993) or H_2 receptors (H_2R; Phelan et al., 1990; Serafin et al., 1993; Wang and Dutia, 1995; Zhang et al., 2008, 2013; Zhuang et al., 2013). Similar findings were observed in neurons in the inferior VN (IVN; Peng et al., 2013). Recent anatomical data have strengthened the histaminergic influence on vestibular functions. Indeed, HA and histidine decarboxylase (HDC) immunoreactive neurons are located exclusively in the tuberomammillary nucleus (TMN) of the hypothalamus (Panula et al., 1984; Watanabe et al., 1984; Pollard and Schwartz, 1987; Airaksinen et al., 1992; Tighilet and Lacour, 1996) and project bilaterally in various regions of the brain (Schwartz et al., 1991), including

the VN (Takeda et al., 1987; Airaksinen and Panula, 1988; Panula et al., 1989). We showed that these histaminergic fibers were sparsely distributed in the whole VN complex of the cat, with a significantly higher density in the MVN and superior VN (SVN) than in the LVN and IVN (Tighilet and Lacour, 1996). The VN complexes contain all types of HA receptors (H_1R, H_2R, and H_3R), as shown with ligand-binding (Bouthenet et al., 1988; Vizuete et al., 1997; Tighilet et al., 2002, 2006, 2007), *in situ* hybridization methods (Ruat et al., 1991; Vizuete et al., 1997; Pillot et al., 2002), and behavioral investigations using VN perfusion with HA receptor ligands (de Waele et al., 1992; Yabe et al., 1993). Local perfusion of the VN on one side with H_2R antagonists or H_3R agonists induces a stereotyped postural and oculomotor syndrome in the guinea pig that mimics that observed after labyrinthectomy (Yabe et al., 1993). In addition, we have showed that vestibular compensation in the cat was strongly accelerated under treatment with H_3R antagonists (betahistine and thioperamide) and that H_3R antagonists induced long-term changes in the expression of HDC mRNA in the TMN and H_3R binding in the VN (Tighilet et al., 1995, 2006, 2007). We have postulated that release of HA likely restores the balance in neuronal activity in the VN cells on both sides, a key mechanism known to promote the vestibular compensation. Finally, histaminergic drugs are widely prescribed for treatment of vertigo and vestibular disorders (Takeda et al., 1986; Fischer, 1991; Redon et al., 2011), suggesting also that HA interferes with the vestibular system and the recovery after a vestibular loss.

The aim of this study was to analyze the plasticity of the histamine H_3R after unilateral vestibular neurectomy (UVN). Since this receptor is the target for HA drugs favoring vestibular compensation (Tighilet et al., 2002), we analyzed the changes in histamine H_3R density in brain networks involved in vestibular function such the VN complex, the TMN, the inferior olive (IO) complex and the solitary nucleus (SN). In addition, we performed [^{3}H]N-α-methylhistamine binding to analyze the affinity of the histamine H_3R for this ligand in control and UVN cats.

MATERIALS AND METHODS

ANIMALS

Experiments were performed on 18 adult domestic cats (3–5 kg) obtained from the "Centre d'élevage du Contigné" (Contigné, France). All experiments were carried out in line with the Animals (scientific procedures) Act, 1986 and associated guidelines, the European Communities Council Directive of 24 November 1986 (86/609/EEC), and the National Institutes of Health guide for the care and use of laboratory animals (NIH publications No. 8023, revised 1978). Every attempt was made to minimize both the number and the suffering of animals used in this experiment. Cats were housed in a large confined space with normal diurnal light variations and free access to water and food. Twelve animals were submitted to UVN and killed at two survival times: 1 ($N = 6$) and 3 weeks ($N = 6$). Six animals were used as a control group. The survival times were selected from our previous behavioral and electrophysiological investigations in the cat, which had showed major postural deficits in acute cats (1 week) and nearly complete recovery in compensated animals (3 weeks; see Lacour et al., 1989).

VESTIBULAR NEURECTOMY

A left side vestibular nerve section was performed under aseptic conditions through a dissecting microscope. Animals were first anesthetized with ketamine (20 mg/kg, i.m.; Rhône-Poulenc, Mérieux, France), received analgesic (Tolfédine, 0.5 ml, i.m.; Vetoquinol, Lure, France), maintained under fluothane anesthesia (2%) and were kept at physiological body temperature using a blanket. The vestibular nerve was sectioned on the left side at a post-ganglion level in order to leave the auditory division intact after mastoidectomy, partial destruction of the bony labyrinth, and surgical exposure of the internal auditory canal (see Xerri and Lacour, 1980 for more details). Animals were maintained under antibiotics for 7 days and analgesics for 3 days. The classical postural, locomotor, and oculomotor deficits displayed by the animals in the days following nerve transection were used as criteria indicating the effectiveness of the vestibular nerve lesion. Completeness of vestibular nerve section had already been assessed by histological procedures in previous studies (Lacour et al., 1976).

TISSUE PREPARATION

Cats of each group were deeply anesthetized with ketamine dihydrochloride (20 mg/kg, i.m., Merial, Lyon, France) and killed by decapitation; after removal from the skull, their brains were cut into several blocks containing the brainstem structures (VN, IO, SN) and the posterior hypothalamic nuclei, and the blocks were rapidly frozen with CO_2 gas. Coronal sections (10-μm-thick) were cut in a cryostat (Leica, Rueil-Malmaison, France), thawed onto "superfrost ++" glass slides (Fisher Scientific, Elancourt, France), and stored at −80°C until radioautography.

H_3 RECEPTOR AUTORADIOGRAPHY

The binding of [^{3}H]N-α-methylhistamine (80 Ci/mmol, NEN^{TM} Life Science Products, Boston, MA, USA) to H_3R was performed on tissue sections as previously described (Cumming et al., 1994a; Tighilet et al., 2002, 2006, 2007). The brain sections (10 μm thick from fresh frozen tissue) were incubated with 4 nM [^{3}H]N-α-methylhistamine, at 4°C in a 150-mM sodium phosphate buffer, pH 7.4, containing 2 mM magnesium chloride, and 100 μM dithiothreitol (Sigma, Saint Quentin, France). The non-specific binding component was measured by adding a large excess of thioperamide (2 mM, Tocris Cookson Ltd, Bristol, UK) 30 min before adding [^{3}H]N-α-methylhistamine. After 45-min incubation, the sections were rinsed three times (each wash lasting 20 s) in the same buffer at 4°C buffer, and then rinsed once in 4°C water for 3 s. The slices were dried with a stream of cold air and exposed to tritium-sensitive film ([^{3}H]Hyperfilm, Amersham). After 9 months of exposure at −80°C, the films were processed in Kodak Industrex developer at room temperature for 2 min, fixed, and then washed. Azure II stained sections were used for reference.

[^{3}H]N-α-METHYLHISTAMINE BINDING ASSAYS

To analyze the affinity of the histamine H_3R for [^{3}H]N-α-methylhistamine in lesioned and control groups of cats, we performed competition experiments. Sections of hypothalamus and brainstem structures, including the VN, the prepositus hypoglossi

(PH), the SN, and the IO of controls, and both 1 and 3 weeks post-lesion cats were homogenized with a Potter homogenizer in 50 mM Tris buffer at pH 7.5, and then the homogenates were centrifuged at 1000 × *g* for 5 min. Protein level was determined according to Bradford (1976).

Hypothalamus and brainstem structure homogenates (250 μg of protein) were incubated with increasing concentrations of thioperamide in the same autoradiographic binding buffer (150 mM sodium phosphate buffer, pH 7.4, containing 2 mM magnesium chloride, and 100 μM dithiothreitol) for 45 min at room temperature in presence of 4 nM of [^{3}H]N-α-methylhistamine. After incubation, 250-μl aliquots were filtrated using a cell harvester, over glass fiber filters (Whatman, GF/B) pre-soaked in 0.3% polyethylenimine. The aliquots were rapidly washed three times with 4 ml of the same buffer. The radioactivity retained by the filters was counted in a beta scintillation analyzer (Packard, Meriden, CT, USA). Curves were fit to the data with Prism non-linear least squares curve-fitting program (GraphPad Software, San Diego, CA, USA). One-site fits were tested.

DATA QUANTIFICATION

H_3 receptor binding measurement

The brainstem and posterior hypothalamic nuclei were identified with Berman's stereotaxic atlas (Berman, 1968; Berman and Jones, 1982). The analysis of IO binding to H_3Rs has been completed in greater detail using Brodal and Kawamura's (1980) monograph. The autoradiograms of the binding to H_3Rs were analyzed and quantified using NIH Image software. [^{3}H] Plastic standards (Amersham) were used to calibrate ^{3}H concentrations. Receptor density was expressed in fmol/mg of protein and evaluated for both the brainstem structures and the TMN. A mean receptor density value was calculated for each nucleus from 60 serial sections. The specific binding value was determined as the difference between total and non-specific binding components for a given area and was evaluated as the mean ± SEM. The density of [^{3}H]N-α-methylhistamine binding sites was evaluated in the following brainstem structures: each of the four main VN (MVN, IVN, SVN, and LVN, respectively), the three subdivisions of the IO (medial accessory, dorsal accessory, and principal nucleus: MIO, DIO, and PIO, respectively), the principal subdivisions of the principal nucleus of the IO [the dorsomedial cell column (DMCC), the dorsal cap (DC), the beta nucleus (β nucleus), the ventrolateral outgrowth (VLO)], the two subdivisions of the SN [lateral and medial nuclei of the solitary tract (SL and SM), PH, and the posterior hypothalamic nuclei]. These last structures included the TMN, the medial mammillary nucleus (MMN), the dorsal hypothalamic area (HDA), the lateral hypothalamic area (HLA), and the posterior hypothalamic area (HPA).

Statistical analysis

Analysis of variance (Super Anova) was used to test the effects of the vestibular lesion (intact versus UVN cats), the survival period (1 week versus 3 weeks), the side (deafferented versus intact), and the structure (VN, the IO and SN subdivisions, the PH, and the posterior hypothalamic nuclei) on H_3R binding density, and to determine the interactions between these variables. Super ANOVA was followed by *post hoc* analysis with the Scheffé test and multicomparison Fisher's test (stateview II software).

RESULTS

All the cats that underwent a left vestibular neurectomy exhibited ocular nystagmus (fast phase directed to the right), head tilt, postural asymmetry, and falling to the left side in the first week following the lesion. Most of them recovered sufficiently in 2 or 3 days to feed by themselves. Those killed at the 3 weeks survival time had shown nearly complete behavioral recovery.

In the control cats, a relatively high [^{3}H]N-α-methylhistamine binding density was found in both the TMN and brainstem nuclei. No significant differences were seen between the left and the right sides and no significant interindividual differences were found in the different groups, as shown by the analysis of variance.

H_3Rs binding density in lesioned cats differed markedly from controls. Repeated-measure analysis of variance demonstrated that group (controls versus lesioned cats) and survival period (1 week versus 3 weeks) constituted the main fixed effects providing the sources of variation among animals. In addition, a significant group × post-lesion time was observed indicating that changes in H_3Rs binding density overtime were different in the two groups of UVN cats.

H_3 RECEPTOR BINDING SITES IN THE CAT POSTERIOR HYPOTHALAMUS

The effects of UVN were examined on the density of histamine H_3Rs in cat brain. [^{3}H]N-α-methylhistamine (4 nM) was used to generate autoradiograms in brain sections in the three groups of cats. Specific binding of [^{3}H]N-α-methylhistamine amounted to 70% of total binding to cat sections. Non-specific binding was homogeneous in the different regions studied.

In the posterior hypothalamus of control cats, the distribution of [^{3}H]N-α-methylhistamine binding sites was heterogeneous. The highest densities (>150 fmol/mg protein) were in the TMN and the MMN. In contrast, the HLA had the lowest binding density (<100 fmol/mg protein). The HDA and the HPA contained moderate levels of binding sites.

Figure 1 shows typical autoradiograms of frontal sections of the posterior hypothalamus from three representative animals either unlesioned (controls: **Figure 1A**) or observed after 1 (**Figure 1B**) or 3 (**Figure 1C**) weeks after UVN. The binding of the agonist [^{3}H]N-α-methylhistamine to H_3R is shown for the controls (**Figure 1A**) as dark stained structures. A high binding density was seen in different areas including the HPA, HLA, and HDA as well as in the TMN and the MMN. Compared to the controls, the UVN induced a bilateral decrease of the binding density in all parts of the posterior hypothalamus including the TMN, with a lower level on the lesioned side compared to the intact side at 1 week post-lesion (**Figure 1B**). This bilateral decrease persisted and became symmetric 3 weeks after the lesion (**Figure 1C**).

The quantitative analysis of the [^{3}H]N-α-methylhistamine binding sites densities in the TMN is shown in the **Figure 2**. The H_3R binding density was 157.5 ± 6.3 fmol/mg of protein on average in the TMN of control cats [150.4 ± 8.6 and 164.5 ± 9.3 on the right and left sides, respectively: Not Statistically Significant (NS)]. In the subgroup of cats examined 1 week after UVN (**Figure 2A**),

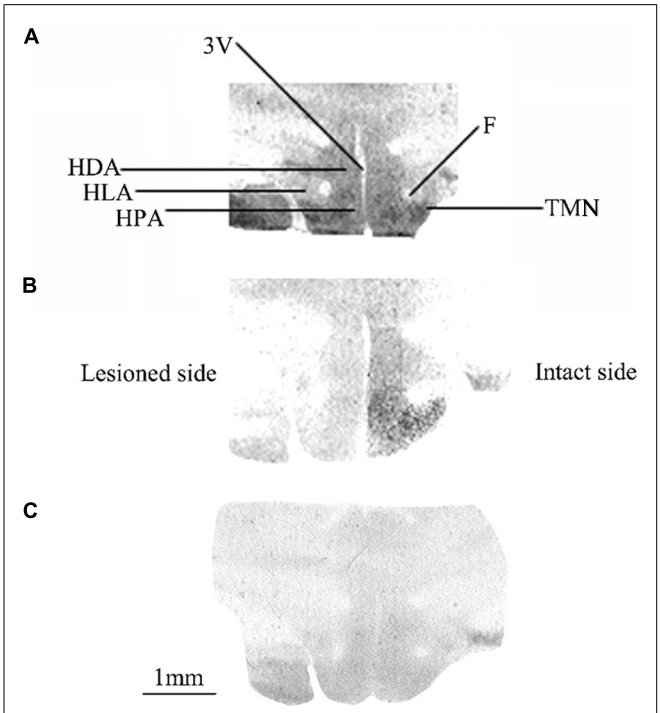


FIGURE 1 | (A–C) [^{3}H]N-α-methylhistamine binding sites in the cat posterior hypothalamus. Coronal sections from three representative control and vestibular-lesioned cats showing decrease of H_3 receptor binding sites in the different structures of the posterior hypothalamus 1 **(B)** or 3 **(C)** weeks after unilateral vestibular neurectomy, as compared to controls **(A)**. HLA, lateral hypothalamic area; HPA, posterior hypothalamic area; HDA, dorsal hypothalamic area; F, fornix; TMN, tuberomammillary nucleus; 3V, third ventricle. Bar: 1 mm.

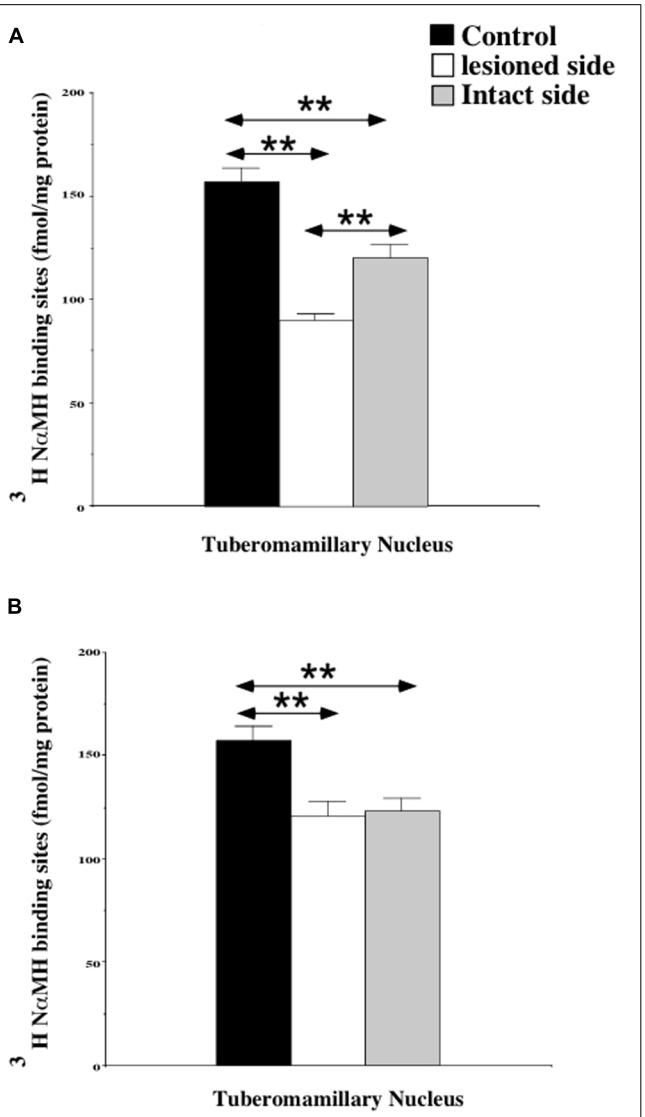


FIGURE 2 | (A,B) Quantification of the effects of a unilateral vestibular neurectomy on the density of [^{3}H]N-α-methylhistamine binding sites in the cat posterior hypothalamus. The [^{3}H]N-α-methylhistamine binding to histamine H_3 receptors is expressed in fmol/mg protein (ordinates) as the mean ± SEM. Data from the tuberomammillary nucleus (TMN) are given as the average value for the right and left structures in the controls (black histograms); they are provided separately for each side [lesioned (thick hatched histograms) versus intact (thin hatched histograms)] for the cats killed 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. $^{**}P < 0.0001$.

the H_3R binding density was significantly decreased in both the lesioned (90.5 ± 0.4; 42%; $P < 0.0001$) and the intact (120.6 ± 6.1; 23%; $P < 0.0001$) sides when compared to the controls. In addition, the H_3R binding density on the lesioned side was significantly lower than that on the intact side (25%; $P < 0.0001$). In the subgroup of cats examined 3 weeks after UVN (**Figure 2B**), there was no significant difference between the intact (123.1 ± 5.8) and the lesioned (120.9 ± 7.1) sides but the [^{3}H]N-α-methylhistamine binding sites densities remained significantly lower than that of the controls (22%; $P < 0.0001$ and 23%; $P < 0.0001$; for the intact and lesioned sides, respectively).

H_3 RECEPTOR BINDING SITES IN THE CAT BRAIN STEM

Figure 3 illustrates the spatial distribution of binding density in representative serial frontal sections collected from the rostral (5.2) to the caudal (11.6) parts of the brainstem in a control cat (**Figure 3A**) and in two representative cats killed 1 (**Figure 3B**) or 3 (**Figure 3C**) weeks after UVN. In the control cat, the pattern of H_3R binding was heterogeneous: highest levels of binding sites were found in the SN complex while lower levels were found in the IO and the VN complexes.

Vestibular complex

The [^{3}H]N-α-methylhistamine binding sites were heterogeneously distributed in the vestibular complex. Among the VN, the MVN and SVN showed the highest level of binding. The IVN showed moderate levels of binding while the lowest level was observed in the LVN. The binding density was also high in the PH nuclei (**Figures 3A–C**). Whatever the stereotaxic reference planes examined, no binding density higher than 150 fmol/mg protein (high level) was present in the vestibular complex.

At 7 days post-lesion, [^{3}H]N-α-methylhistamine binding site density significantly decreased on the deafferented side in several

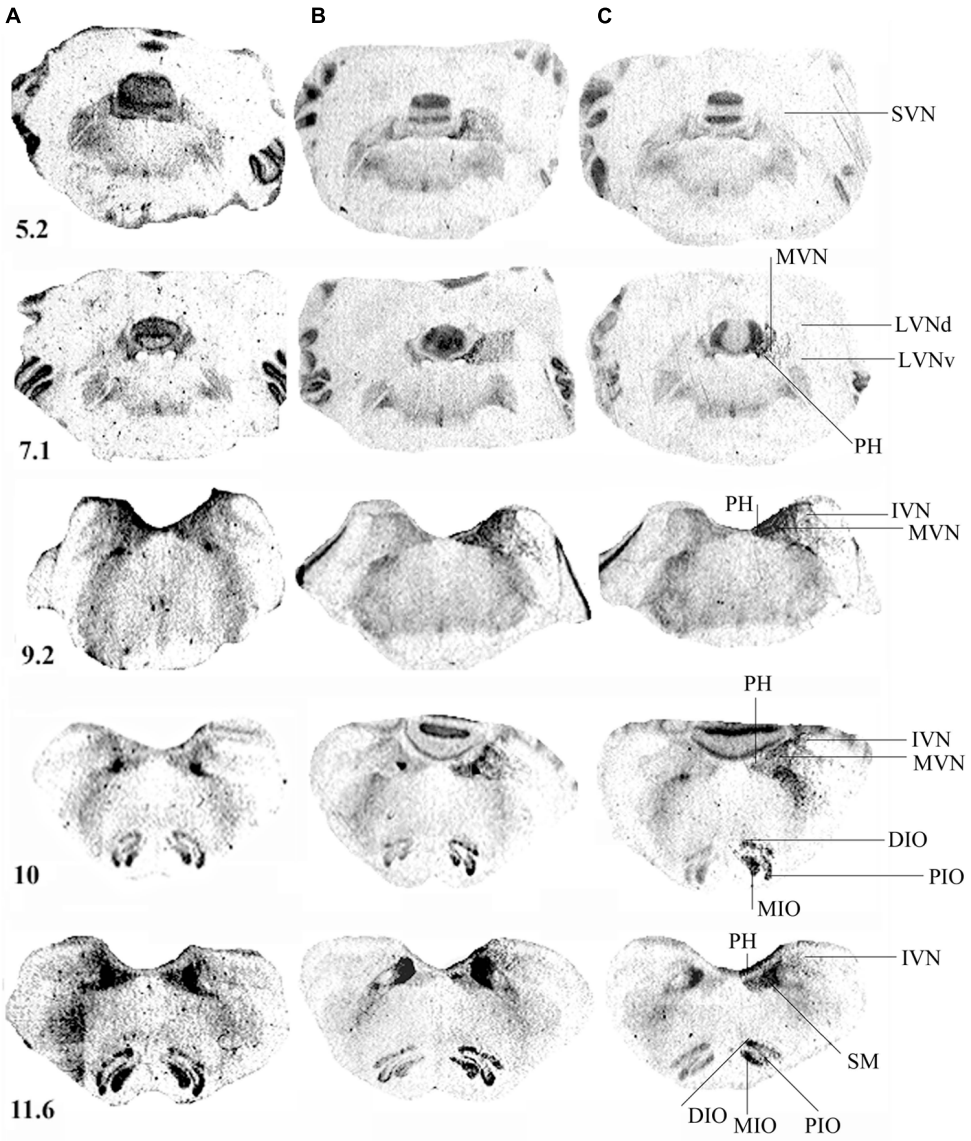


FIGURE 3 | (A–C) [^{3}H]N-α-methylhistamine binding sites in the cat brainstem. Coronal sections from three representative control and unilateral vestibular neurectomized cats showing decreases in histamine H_3 receptor binding in the different structures of the brainstem on the lesioned side (left side in the figure) 1 **(B)** or 3 **(C)** weeks after unilateral vestibular neurectomy, as compared to the controls **(A)**. Illustrations are given for serial sections collected from the rostral (5.2) to the caudal (12.1) parts of the brainstem. IVN, inferior vestibular nucleus; LVNd and v, lateral vestibular nucleus, dorsal and ventral parts; MVN, medial vestibular nucleus; SVN, superior vestibular nucleus; PH, prepositus hypoglossi; DIO, MIO, and PIO, dorsal, medial, and posterior parts of the inferior olive, respectively; SM, medial part of the solitary tract. Bar: 1 mm.

nuclei relative to the controls: the PH (11%; $P < 0.0001$), the MVN (13.5%; $P < 0.0001$), and the SVN (16%; $P < 0.001$; see **Figures 3B** and **4A**). The binding remained unchanged in the other VN (LVN and IVN).

Bilateral changes in [^{3}H]N-α-methylhistamine binding site density were observed in the VN complexes 21 days after UVN. The lesion induced a significant bilateral decrease with an ipsilateral predominance in the PH (26 and 14%; $P < 0.0001$) and the MVN (24 and 10%; $P < 0.0001$) on the lesioned and intact sides respectively (see **Figures 3C** and **4B**). The binding site density remained unchanged for the LVN and SVN.

Inferior olive complex

Figure 3 illustrates the distribution of [^{3}H]N-α-methylhistamine binding sites in the IO complex. In control cats, the binding signals were observed in all subregions but the intensity of signals varied markedly between the subregions. Moderate H_3R binding was detected in the DMCC, the DC, and the VLO while strong binding was observed in the β nucleus, the MIO, the DIO, and the PIO.

At 7 days post-lesion, the density of [^{3}H]N-α-methylhistamine receptor binding was significantly lower on the ispsilateral side compared to the controls and the contralateral side in the MIO (35 and 31%; $P < 0.0001$, respectively), the DIO (23 and 17%;

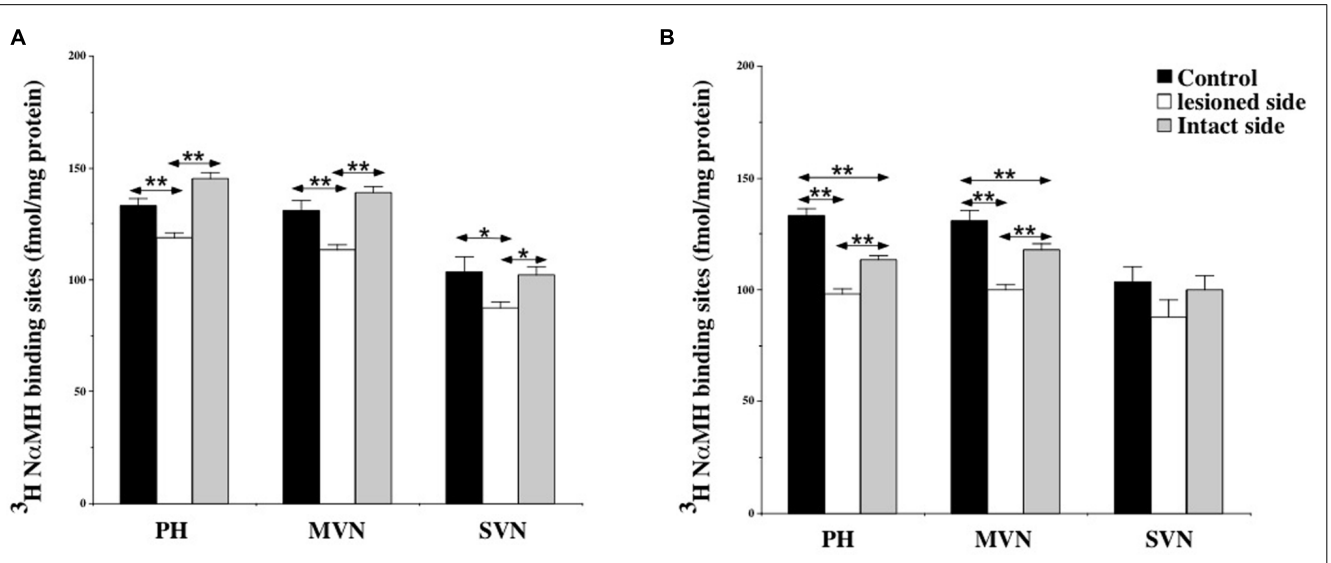


FIGURE 4 | (A,B) Effects of a unilateral vestibular neurectomy on the density of [^{3}H]N-α-methylhistamine binding sites in the vestibular nuclei and the prepositus hypoglossi. Changes in histamine H_3 receptor binding in the vestibular nuclei and the prepositus hypoglossi 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. Quantitative analysis is expressed as mean values and standard errors of femtomole of [^{3}H]N-α-methylhistamine specifically bound per milligram of protein from autoradiograms. Data from the prepositus hypoglossi (PH), and the medial (MVN) and superior (SVN) vestibular nuclei are given as the average value of the right and left structures for the controls (black histograms); they are provided separately for each side [lesioned (thick hatched histograms) versus intact (thin hatched histograms)] for the cats killed 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. $*P < 0.001$, $**P < 0.0001$.

$P < 0.0001$), and the PIO (41 and 28%; $P < 0.0001$). In contrast, binding sites densities in the IO nuclei on the contralateral side were unchanged, except that the PIO showed lower values (19%; $P < 0.0001$; **Figure 5A**).

As shown for the VN, bilateral changes in [^{3}H]N-α-methylhistamine binding site density were detected in the three subdivisions of the IO 21 days after UVN. The lesion induced a significant bilateral decrease in the MIO (42 and 27%; $P < 0.0001$), the DIO (38 and 20%; $P < 0.0001$) and the PIO (58 and 40%; $P < 0.0001$) on the lesioned and intact sides, respectively (**Figure 5B**). The lesioned side was more greatly reduced than the intact side (24%; $P < 0.0001$; 22%; $P < 0.0001$, and 25%; $P < 0.0001$ for the MIO, DIO, and the PIO, respectively).

Except for the DMCC which remained unaffected by the vestibular lesion, bilateral changes in [^{3}H]N-α-methylhistamine binding site density were detected in the main subdivisions of the PIO (DC, VLO and β nucleus) 1 and 3 weeks after UVN. In addition, these later subdivisions, showed a significant decrease on the lesioned side when compared to the intact side at the two survival periods (**Figures 6A,B**).

Solitary nucleus

Among the structures analyzed in this study, the SN showed the highest H_3 binding density. The binding was about 400 fmol/mg protein in the SM and 100 fmol/mg protein in the SL.

At 7 days post-lesion, the density of [^{3}H]N-α-methylhistamine receptor binding was significantly lower on the ispsilateral side (**Figure 7A**) compared to the controls and the contralateral side in the SM (22 and 24%; $P < 0.0001$, respectively) and the SL (18 and 25%; $P < 0.0001$, respectively). The binding regained control values 3 weeks after the lesion (**Figure 7B**).

COMPETITION BETWEEN [^{3}H]N-α-METHYLHISTAMINE AND THIOPERAMIDE ON HOMOGENATES OF CONTROL AND VESTIBULAR-LESIONED CAT HYPOTHALAMUS AND BRAINSTEM

Table 1 shows the specific binding of [^{3}H]N-α-methylhistamine (4 nM) in the hypothalamus and brainstem structure homogenates of the three groups of cats. As shown previously for the TMN (Tighilet et al., 2002), [^{3}H]N-α-methylhistamine binding was significantly ($P < 0.05$) reduced bilaterally in the hypothalamus at 1 week post-lesion, with a predominant down-regulation in the lesioned side (28%) compared to the intact side (26%). A significant bilateral and symmetric reduction was observed at 3 weeks post-lesion (28 and 31% in the intact and lesioned sides, respectively, $P < 0.05$).

For the brainstem, binding on the lesioned side was significantly lower than on the intact side 1 week and 3 weeks after the lesion (30 and 29%, respectively, $P < 0.05$). In comparison with the controls, the binding was significantly decreased on the lesioned side only at 1 week (30%, $P < 0.05$); it was significantly reduced for both lesioned and intact sides at 3 weeks (43 and 21%, $P < 0.05$). The reductions were in the same range as that observed in the autoradiographic study.

Increasing concentrations of thioperamide gradually inhibited [^{3}H]N-α-methylhistamine specific binding in hypothalamus (**Figures 8A,B**) and brainstem homogenates (**Figures 8C,D**). Under our binding conditions, similar to those of the autoradiographic procedures with the presence of sodium ions, the concentration of thioperamide inducing 50% inhibition of

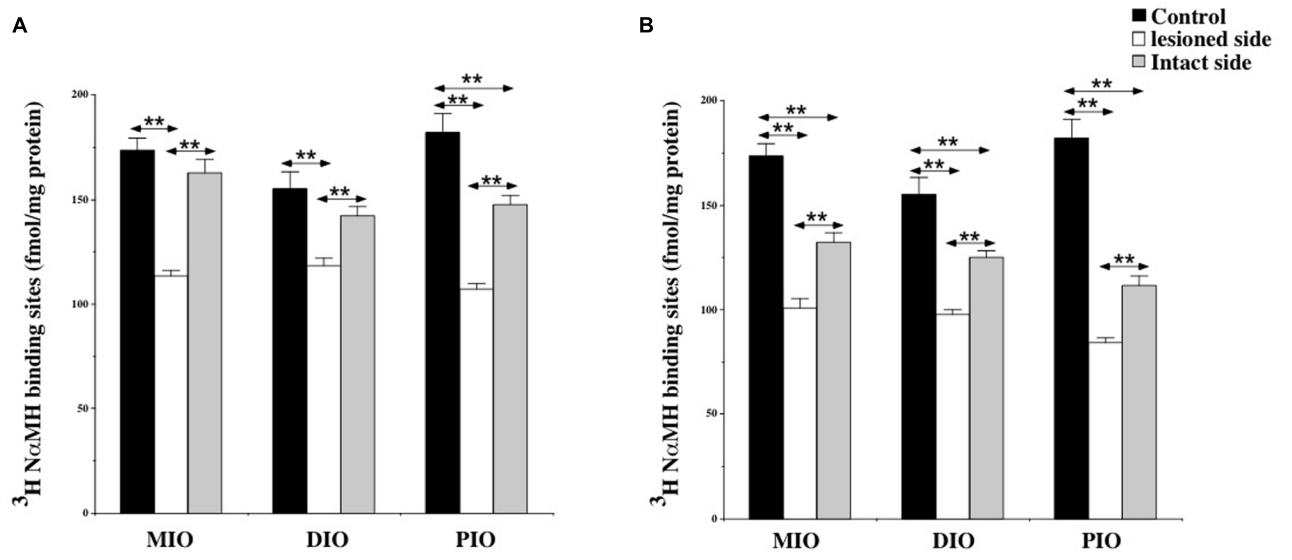


FIGURE 5 | (A,B) Effects of a unilateral vestibular neurectomy on the density of [^{3}H]N-α-methylhistamine binding sites in the three parts of the inferior olive. Changes in histamine H_3 receptor binding in the inferior olive 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. Results are expressed as mean values and standard errors of femtomole of [^{3}H]N-α-methylhistamine specifically bound per milligram of protein from autoradiograms. Data from the medial (MIO), the dorsal (DIO), and the posterior (PIO) parts of inferior olive are given as the average value of the right and left structures for the controls (black histograms); they are provided separately for each side [lesioned (thick hatched histograms) versus intact (thin hatched histograms)] for the cats killed 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. $^{**}P < 0.0001$.

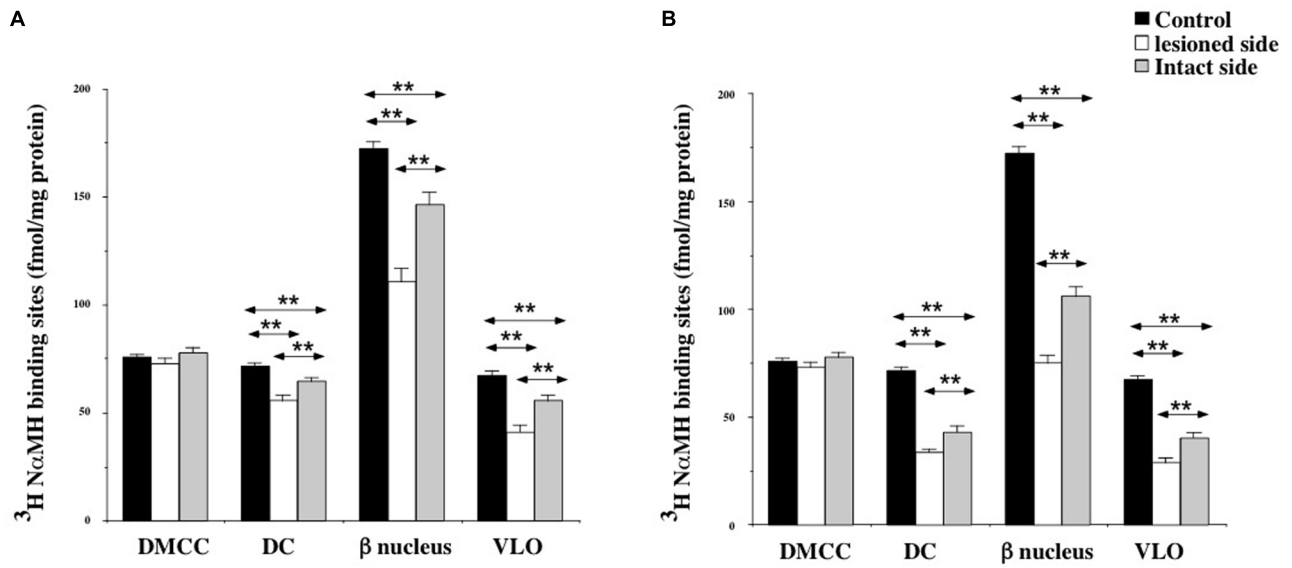


FIGURE 6 | (A,B) Effects of a unilateral vestibular neurectomy on the density of [^{3}H]N-α-methylhistamine binding sites in the different subregions of the PIO. Changes in histamine H_3 receptor binding in the different subregions of the PIO 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. Results are expressed as mean values and standard errors of femtomole of [^{3}H]N-α-methylhistamine specifically bound per milligram of protein from autoradiograms. Data from the dorsomedial cell column (DMCC), the dorsal cap (DC), the beta nucleus (b nucleus) and the ventrolateral outgrowth (VLO) are given as the average value of the right and left structures for the controls (black histograms); they are provided separately for each side [lesioned (thick hatched histograms) versus intact (thin hatched histograms)] for the cats killed 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. $^{**}P < 0.0001$.

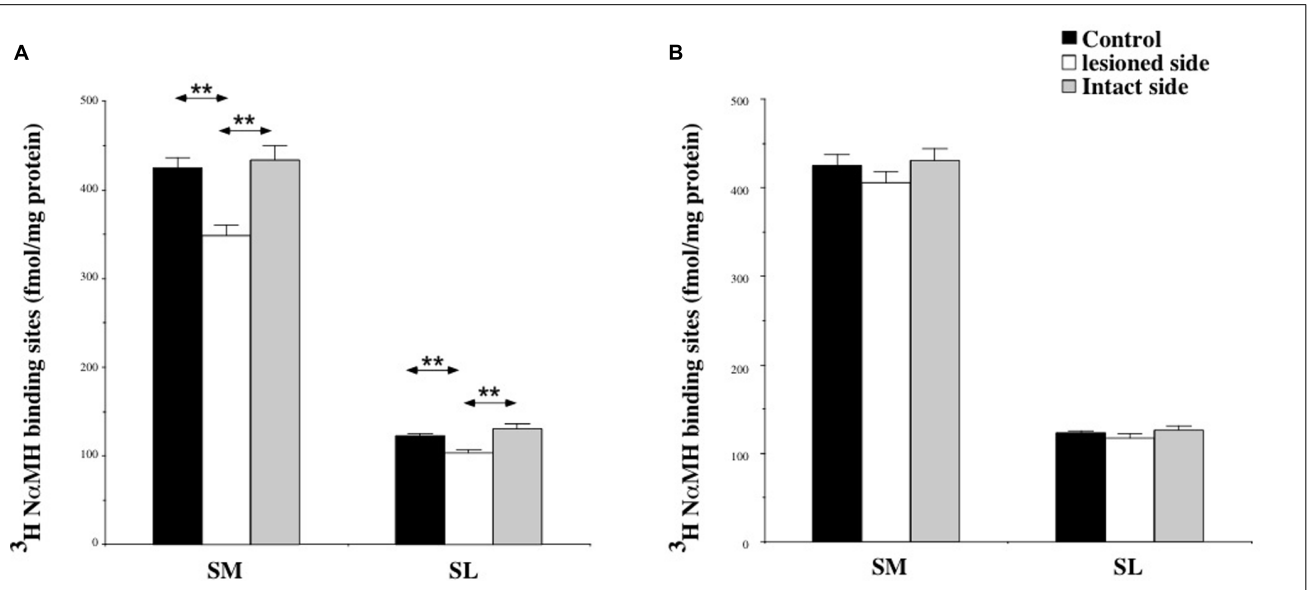


FIGURE 7 | (A,B) Effects of a unilateral vestibular neurectomy on the density of [^{3}H]N-α-methylhistamine binding sites in the two subdivisions of the solitary nucleus complex. Changes in histamine H_3 receptor binding in the two subdivisions of the SN 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. Results are expressed as mean values and standard errors of femtomole of [^{3}H]N-α-methylhistamine specifically bound per milligram of protein from autoradiograms. Data from the lateral nucleus of the solitary tract (SL), and the medial nucleus of the solitary tract (SM) are given as the average value of the right and left structures for the controls (black histograms); they are provided separately for each side [lesioned (thick hatched histograms) versus intact (thin hatched histograms)] for the cats killed 1 **(A)** or 3 **(B)** weeks after unilateral vestibular neurectomy. $^{**}P < 0.0001$.

Table 1 | [^{3}H]N-α-methylhistamine binding in the lesioned versus control cats.

Cat group	Mean ± SEM	
	1 Week	3 Weeks
Hypothalamus		
Control	41.65 ± 1.38	
Intact side	41.66 ± 1.35	39.84 ± 1.14
Lesioned side	29.96*[a] ± 1.52	27.81*[a] ± 1.86
Brainstem		
Control	45.39 ± 1.73	
Intact side	45.78 ± 1.56	36.02[a] ± 0.75
Lesioned side	32.08*[a] ± 0.33	25.91*[a] ± 0.44

[^{3}H]N-α-methylhistamine (4 nM) was incubated with hypothalamus and brainstem homogenates (250 μg protein) in the same autoradiography binding buffer for each group of cats. The [^{3}H]N-α-methylhistamine binding is expressed in fmol/mg of protein.

**P < 0.05, Student's t-test, comparison with intact side.*

[a] *P < 0.05, Student's t-test, comparison with control animals.*

[^{3}H]N-α-methylhistamine binding (IC_{50}) was 1.92 ± 1.65 and 1.00 ± 1.56 nM in control cats ($N = 3$) for the hypothalamus and the brainstem, respectively. The IC_{50} in the cats 1 week after vestibular lesion ($N = 3$) were 0.85 ± 1.41 (intact side) and 4.5 ± 1.37 (lesioned side) for the hypothalamus, and 0.98 ± 1.61 (intact side) and 0.3 ± 1.38 (lesioned side) for the brainstem. Three weeks after lesion, the IC_{50} of cats ($N = 3$) were 1.14 ± 1.5 and 1.67 ± 1.71 for the ipsilateral and contralateral hypothalamus, respectively, and 0.66 ± 1.61 and 2.13 ± 1.82 for the brainstem on the intact and lesioned sides, respectively. The statistical analysis on these IC_{50} values showed no changes in the affinity of thioperamide for H_3Rs in competition with [^{3}H]N-α-methylhistamine, i.e., no change in IC_{50} value of the radioligand whatever the groups of cats.

DISCUSSION

Unilateral vestibular neurectomy induced a bilateral decrease in binding of the agonist [^{3}H]N-α-methylhistamine to H_3R in the TMN at 1 week post-lesion, with a predominant down-regulation in the ipsilateral TMN. The bilateral decrease remained at the 3 weeks survival time and became symmetric. Concerning brainstem structures, N-α-methylhistamine binding in the VN, the PH and the different subdivisions of the IO decreased unilaterally on the ipsilateral side at 1 week and bilaterally 3 weeks after UVN with an ipsilateral predominance. Similar changes were observed in the subdivisions of the SN only 1 week after the lesion. These findings indicate a vestibular lesion-induced plasticity of the H_3Rs, which could contribute to vestibular function recovery.

DISTRIBUTION OF THE H_3Rs BINDING SITES

The distribution of H_3Rs binding evidenced by autoradiographic studies in various species (rat, Cumming et al., 1991; Pollard et al., 1993; Anichtchik et al., 2000; guinea pig, Cumming et al., 1994b; mouse, Cumming et al., 1994b; Janssen et al., 2000; primate and human, West et al., 1999) showed a wide and heterogeneous distribution of H_3Rs binding sites in various brain areas (cerebral cortex,

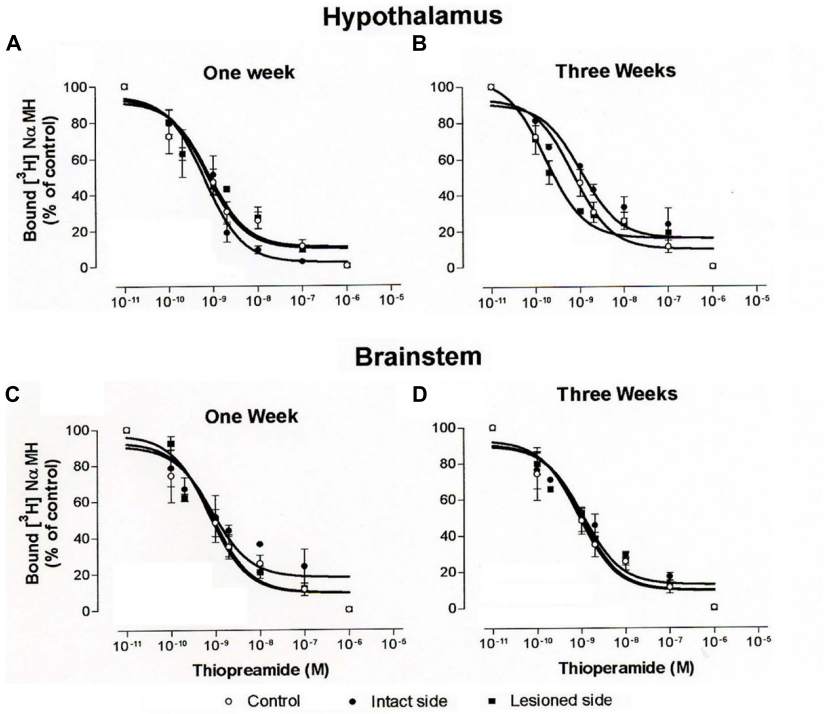


FIGURE 8 | (A–D). Binding of [^{3}H]N-α-methylhistamine. Competition curves obtained from binding experiments involving [^{3}H]N-α-methylhistamine and increasing concentrations of thioperamide in hypothalamus **(A,B)** and brainstem **(C,D)** homogenates from control cats and vestibular-lesioned cats killed 1 **(A,C)** and 3 **(B,D)** weeks after lesion.

hippocampal formation, hypothalamus, TMN,. . . and lower brain stem areas: for review, see Schwartz et al., 1991). Our autoradiographic investigation confirms this heterogeneous distribution in the cat brain stem (IO, PH, VN, SN) and diencephalon (posterior hypothalamus). The H_3Rs binding distribution reflects the distribution of histaminergic nerve terminals in the VN complex, with H_3Rs binding site density higher in the MVN and the SVN than in the LVN and IVN (Tighilet and Lacour, 1996). However, the HA-labeled fibers and varicosities in the VN were much less dense than in the TMN (Tighilet and Lacour, 1996, 1997), while the density of the H_3Rs binding sites was similar in these structures. This finding suggests that the H_3Rs in the VN are composed of both auto and heteroreceptors and that the H_3 heteroreceptors located on non-histaminergic afferents or on vestibular perikarya, as recently shown by Pillot et al. (2002) would predominate.

EFFECTS OF UNILATERAL VESTIBULAR LESION ON H_3Rs BINDING SITES

The UVN produced a significant reduction in [^{3}H]N-α-methylhistamine binding in the VN, the PH as well as the different subdivisions of the IO and the SN. This reduction was observed only on the deafferented side at 1 week but bilaterally 3 weeks after UVN, with an ipsilateral predominance. It could be caused by a down-regulation of the histamine H_3Rs or a change in the affinity of the radioligand for the H_3Rs. Our findings in competition studies with thioperamide did not show significant changes in IC_{50} values of the [^{3}H]N-α-methylhistamine radioligand to H_3Rs in UVN cats, strengthening the hypothesis of a down-regulation of the histamine H_3Rs.

Several hypotheses can explain this down-regulation. The first concerns the presynaptic histamine H_3 autoreceptors and heteroreceptors in the VN complex. The changes found 1 week after UVN can be explained by the bilateral anatomical connections between the VN complexes and the posterior hypothalamus strengthening the idea of vestibulo-hypothalamic loop activation due to VNC electrical asymmetry. Indeed, the MVN project bilaterally to the posterior hypothalamus (Ericson et al., 1991) but direct and predominantly contralateral projections from the MVN to the HPA have been found in the monkey (Matsuyama et al., 1996). While the posterior hypothalamus sends histaminergic fibers to the ipsilateral MVN (Pollard and Schwartz, 1987). The asymmetrical firing rate of the VN cells in acute UVN cats (1 week), with reduced activity on the lesioned side and increased activity on the intact side for both the MVN (Precht et al., 1966) and the LVN (Zennou-Azogui et al., 1993) can therefore account for the HDC mRNA up-regulation, particularly pronounced in the TMN at 1 week post-lesion on the lesioned side (Tighilet et al., 2006). The time-course of HDC mRNA expression in the TMN of the UVN cats correlates with electrophysiological data. Electrophysiological investigations in the UVN cat still revealed, 3 weeks post-lesion, asymmetrical spontaneous firing rates between the bilateral VNCs, but the imbalance was attenuated. This attenuated imbalance may account for the lower asymmetry in HDC mRNA expression observed between the two TMN at this stage (Tighilet et al.,

2006, 2007). Therefore, and as previously discussed (Tighilet et al., 2002), the autoradiographic [^{3}H]N-α-methylhistamine binding reduction very likely results from a down-regulation of the histamine H_3 receptors. One week after UVN, the high level of histamine synthesis in the ipsilateral TMN (Tighilet et al., 2006) and release in the ipsilateral VN (Tighilet and Lacour, 1997) due to vestibular lesion very likely leads to a high desensitization of the histamine H_3 receptor, its internalization and degradation in the deafferented VN. Based on the data obtained by *in situ* hybridization and electrophysiology, this reduction was observed bilaterally 3 weeks after UVN, with an ipsilateral predominance in the same brainstem structures. Such molecular mechanisms have been demonstrated in the guinea pig ileum for the histamine H_3R (Perez-Garcia et al., 1998) and in a specific cell line for the histamine H_2R (Fukushima et al., 1997).

Activity-dependent plasticity is a second hypothesis accounting for the H_3Rs binding asymmetries. As reported above, the second-order vestibular neurons on the deafferented side (type I) lose their major excitatory input after UVN and become silent, while those on the intact side show a slightly increased resting discharge. The H_3Rs down-regulation at 1 and 3 weeks post-lesion could result from this decreased activity, at least on the lesioned side since receptors expression can be activity dependent (Tighilet et al., 1998). This cannot, however, explain the binding sites reduction seen contralaterally at 3 weeks since VN activity on the intact side is near normal at least for the type I neurons. The effect observed on the contralateral VN may mainly concern other populations of VN cells like GABA interneurons (Tighilet and Lacour, 2001). A third hypothesis could be that the primary vestibular afferents, which constitute the vestibular nerve, could carry in their terminals H_3 receptors that disappear with the degenerative fibers induced by the nerve section. In line with this hypothesis, recent data reported the presence of H_3 receptors in neurons of mouse Scarpa's ganglion (Tritto et al., 2009).

The H_3Rs binding site density was roughly similarly modified in all part of the posterior hypothalamus including the TMN and the subdivisions of the IO, with ipsilateral and bilateral binding reductions at 1 and 3 weeks after UVN, respectively. Concerning the SN, the binding decrease was observed exclusively on the lesioned side at 1 week after UVN. Mechanisms similar to the first hypothesis postulated below for the VN are the most appropriate to interpret this result since HA-like immunoreactive afferent fibers were found in the TMN (Tighilet and Lacour, 1996), the SN and IO complexes in the cat (unpublished data) and the rabbit IO (Iwase et al., 1993).

However, our results are in conflict with a recent report describing the changes in histamine H_1, H_2, and H_3 receptors expression in the rat MVN and flocculus after unilateral labyrinthectomy (UL; Zhou et al., 2013). Using quantitative real-time PCR, western blotting and immunohistochemistry, these authors showed an up-regulation of all HA receptors on the first and third day after UL in the ipsilesional flocculus, and on the first day in the ipsilesional MVN compared to the sham controls as well as the contralateral side. The mRNA and protein levels of H_1, H_2, and H_3 receptors returned to basal levels at 3 days (MVN) and 7 days (flocculus) after UL. By performing *in situ* hybridization in UL rats, Lozada et al. (2004) found also an increase in the mRNA levels of H_3 receptor isoforms in the MVN on the first day after UL. Such discrepancy between the data might be due first to the surgical approach. We have demonstrated that the recovery mechanisms and the cellular plastic events occurring in the VN are different after UL and UVN in the cat model (Lacour et al., 2009; Dutheil et al., 2011). It might depend also on the animal species tested. Indeed, the temporal changes in the static vestibular deficits are different in the rat (behavioral recovery achieved within 1 week) compared to the cat (behavioral recovery requires a longer time period: 6 weeks).

HISTAMINE H_3 RECEPTORS PLASTICITY, VESTIBULAR COMPENSATION, AND PHARMACOLOGICAL IMPLICATIONS

The interesting point of this investigation is the functional role of such H_3R plasticity in the vestibular compensation. It is well established that the restoration of vestibular functions is subtended by a physiological model involving restoration of balanced electrical activity between homologous VN. Does the H_3R plasticity constitute a neurochemical mechanism involved in the recovery of a balanced electric activity between homologus VN?

The H_3 receptor binding asymmetries observed in the VN and in the PH in the acute stage of vestibular compensation (7 days) are correlated with those seen behaviorally and electrophysiologically (Smith and Curthoys, 1989) at this time. These asymmetries persist at the compensated stage (3 weeks) in the MVN and the PH, but these nuclei exhibited also a significant bilateral decrease compared to the controls. The H_3Rs binding changes observed in the MVN and the PH 3 weeks after UVN can be seen as a long-term plastic change involved in regulating sensitivity of the second-order vestibular cells on both sides with a higher effect on the lesioned side. Intracellular recordings from neurons in the MVN have revealed several classes of neurons, all of which are depolarized by histamine via an action at postsynaptic H_1 (Inverarity et al., 1993) or H_2 receptors (Phelan et al., 1990; Serafin et al., 1993; Wang and Dutia, 1995). If we consider the presynaptic H_3 autoreceptors located on histaminergic terminals innervating the VN, particularly the MVN (Takeda et al., 1987; Steinbusch, 1991; Tighilet and Lacour, 1996), their bilateral down-regulation observed in the MVN at 3 weeks could produce an increase in histamine synthesis and release in this nucleus on both sides, contributing to rebalance the bilateral activity and thus favoring the behavioral recovery process. Interestingly, recent data using H_3 receptor gene transcript have demonstrated the presence of high levels of H_3 receptors mRNA on vestibular perikarya themselves including the MVN (Pillot et al., 2002). As postulated by these authors, besides autoreceptors, these H_3 receptors may explain that systemic administration of H_3 receptor antagonists or inverse agonists strongly decrease the horizontal vestibular-ocular reflex in the guinea pig (Yabe et al., 1993) and facilitate vestibular compensation in the cat (Tighilet et al., 1995), thereby suggesting the potential interest of these compounds as anti-vertigo drugs.

H_3 RECEPTORS, NEUROTRANSMISSION, AND VESTIBULAR COMPENSATION

Since the original demonstration by Arrang et al. (1983) that histamine H_3 receptors inhibit histamine synthesis and release, histamine has been found to inhibit the release of many

other transmitters via this receptor, including glutamate (Brown and Reymann, 1996), GABA (Jang et al., 2001), noradrenaline (Schlicker et al., 1989), dopamine (Schlicker et al., 1993), acetylcholine (Arrang et al., 1995), serotonin (Schlicker et al., 1988), and various peptides (Hill et al., 1997). Interestingly, these different classes of neurotransmitters are present in the VN and are involved in both vestibular functions and vestibular compensation (de Waele et al., 1995). Let us consider the GABAergic system, the glutamatergic system and the H_3 receptors location in the MVN: (1) on histaminergic fibers or other afferents fibers innervating the MVN. (2) On terminals of the inhibitory interneurons in the MVN that make synaptic contacts on second-order excitatory neurons. (3) On the terminals of second-order excitatory MVN neurons making cross-commissural synaptic contacts on contralateral MVN inhibitory interneurons. After UVN, down-regulation of the H_3 receptors in the MVN could facilitate GABA release from cerebellar inputs and from inhibitory interneurons that make synaptic contacts with second-order neurons, or facilitate glutamate release from terminals of second-order MVN neurons that synapse on inhibitory interneurons in the contralateral MVN. Modulation of GABAergic and glutamatergic by the H_3R should restore the balance between the VN on both sides.

H_3 RECEPTOR PLASTICITY IN THE TMN

Unilateral vestibular neurectomy induced an up-regulation of HDC mRNA expression in the TMN resulting from an activation of a vestibulo-hypothalamo-vestibular loop. The mechanism of action of histamine on to the VN helps to explain the functional role of this neural loop activated when asymmetrical inputs reach the central vestibular structures (Horii et al., 1993). This loop could convey signals that promote the regulation of HDC gene expression leading to the release of histamine in the VN. The modulatory action of histamine could intervene in rebalancing the activity between homologous VN to facilitate the behavioral recovery.

H_3Rs binding changes observed in the TMN at both stages of vestibular compensation could regulate the activity of these nuclei. Indeed, it has been shown that activation of H_3 receptors on TMN neurons inhibits multiple high-threshold calcium channels (Takeshita et al., 1998) leading to an inhibition of their firing rate (Haas, 1992). The bilateral decrease of the H_3Rs observed in these nuclei would activate their firing rate, inducing probably the up-regulation of HDC mRNA expression observed after UVN at these two stages (Tighilet et al., 2006). Bilateral down-regulation of H_3R located on terminals of histaminergic TMN neurons that synapse with other TMN neurons should increase the HA synthesis and release.

HISTAMINERGIC SYSTEM PLASTICITY IN THE IO AND THE SN

The IO subdivisions showed H_3 binding changes similar to that observed in the VN and the PH. The olivo-cerebellar projections are known to be indispensable for vestibular compensation. Indeed, electrolytic and chemical lesions of the IO prevents vestibular compensation and causes reappearance of UL symptoms after the vestibular compensation has been established (Llinas et al., 1975). It has also been reported that UL or UVN induces expression of plasticity markers such immediate early genes (Kaufman et al., 1992; Cirelli et al., 1996; Sato et al., 1997; Gustave Dit Duflo et al., 1999) and Brain Derived Neurotrophic Factor gene (Li et al., 2001) in the IO. The down-regulation of H_3 receptor binding sites observed unilaterally at 1 week and bilaterally at 3 weeks in the different subdivisions of the IO could be the result of an increased histamine release originating from the TMN. Functionally, by its action on IO neurons Histamine could reorganize both the olivo-vestibular and the olivo-cerebellar systems involved in the oculomotor and the postural recovery.

Concerning the vestibulo-solitary pathways, both anatomical and electrophysiological studies have shown that the solitary nucleus receives input from the vestibular nuclei that participate in vestibulo-sympathetic reflexes (Yates et al., 1994). Since the SM receives dense gastrointestinal input (Norgren, 1978; Leslie et al., 1982; Shapiro and Miselis, 1985), H_3Rs binding asymmetry observed in this nucleus 1 week after UVN may reflect the increased salivation, retching, and emesis which are present at this post-lesional delay.

PHARMACOLOGICAL IMPLICATIONS

Whether H3 receptors plasticity plays a significant role in the recovery process is a question of interest for a better understanding of vestibular compensation and for pharmacological applications to vestibular pathology. HA has been largely used for treatment of vertigo and disturbances of the inner ear assumed to be of vascular origin (Fischer, 1991). Betahistine is a structural analog of HA that is effective also in vestibular syndromes unrelated to vascular insufficiency like peripheral vestibular disorders (Canty and Valentine, 1981; Oosterveld, 1984) and Menière's disease (Frew and Menon, 1976; Bertrand, 1982). We previously showed that behavioral recovery after UVN in our cat model was strongly accelerated by betahistine (Tighilet et al., 1995). We also demonstrated that this drug induced an up-regulation of HDC mRNA in the TMN and a reduction of [^{3}H]N-α-methylhistamine labeling in both the TMN, the VN complex, and the three IO subnuclei (Tighilet et al., 2002). Hence, vestibular lesion as well as treatment with a structural HA analog induce similar plastic changes of the histaminergic system (H_3R), strengthening the hypothesis that HA may elaborate and maintain the vestibular compensation process. Taken together, our results also point to the potential interest of compounds like H_3Rs antagonists or inverse agonists (Morisset et al., 2000) as anti-vertigo drugs.

In conclusion, our study shows that UVN induces robust changes in H_3 receptors binding at the different stages of the vestibular compensation in the cat. These changes are observed not only in the VN but also in other central nervous system (CNS) structures such the PH, the TMN, and the IO supporting the view of Llinas and Walton (1979) that vestibular compensation is a distributed property of the CNS. This result strengthens the hypothesis that histamine could be a preferential candidate in the elaboration and the maintenance of vestibular compensation process. The specific target of histamine in vestibular recovery is the H_3 auto and/or heteroreceptors located on different brain structures, including the VN. This H_3R target would additionally lead to positive side effects on the

behavioral recovery by increasing the vigilance level and improving post-lesion sensorimotor activity and cognitive functions (Brioni et al., 2011).

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Biases in the perception of self-motion during whole-body acceleration and deceleration

Luc Tremblay[1], Andrew Kennedy[1], Dany Paleressompoulle[2], Liliane Borel[2,3], Laurence Mouchnino[2,4] and Jean Blouin[2,4]*

[1] Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, ON, Canada
[2] Fédération de Recherche 3C Comportement-Cerveau-Cognition, Centre National de la Recherche Scientifique – Aix-Marseille University, Marseille, France
[3] Laboratoire de Neurosciences Intégratives et Adaptatives, Centre National de la Recherche Scientifique – Aix-Marseille University, Marseille, France
[4] Laboratoire de Neurosciences Cognitives, Centre National de la Recherche Scientifique – Aix-Marseille University, Marseille, France

Edited by:
Pierre Denise, Université de Caen Basse–Normandie, France

Reviewed by:
Michael Barnett-Cowan, Western University, Canada
Matthias Hartmann, University of Bern, Switzerland

***Correspondence:**
Jean Blouin, Laboratoire de Neuroscience Cognitives, Centre National de la Recherche Scientifique – Aix-Marseille Université, 3 Place Victor Hugo, 13331 Marseille, France
e-mail: jean.blouin@univ-amu.fr

Several studies have investigated whether vestibular signals can be processed to determine the magnitude of passive body motions. Many of them required subjects to report their perceived displacements offline, i.e., after being submitted to passive displacements. Here, we used a protocol that allowed us to complement these results by asking subjects to report their introspective estimation of their displacement continuously, i.e., during the ongoing body rotation. To this end, participants rotated the handle of a manipulandum around a vertical axis to indicate their perceived change of angular position in space at the same time as they were passively rotated in the dark. The rotation acceleration (Acc) and deceleration (Dec) lasted either 1.5 s (peak of 60°/s^2, referred to as being "High") or 3 s (peak of 33°/s^2, referred to as being "Low"). The participants were rotated either counter-clockwise or clockwise, and all combinations of acceleration and deceleration were tested (i.e., AccLow-DecLow; AccLow-DecHigh; AccHigh-DecLow; AccHigh-DecHigh). The participants' perception of body rotation was assessed by computing the gain, i.e., ratio between the amplitude of the perceived rotations (as measured by the rotating manipulandum's handle) and the amplitude of the actual chair rotations. The gain was measured at the end of the rotations, and was also computed separately for the acceleration and deceleration phases. Three salient findings resulted from this experiment: (i) the gain was much greater during body acceleration than during body deceleration, (ii) the gain was greater during High compared to Low accelerations and (iii) the gain measured during the deceleration was influenced by the preceding acceleration (i.e., Low or High). These different effects of the angular stimuli on the perception of body motion can be interpreted in relation to the consequences of body acceleration and deceleration on the vestibular system and on higher-order cognitive processes.

Keywords: vestibular, perception, body rotation, head rotation, passive motion, acceleration, deceleration, velocity storage

INTRODUCTION

The study of space perception and navigation has devoted a great deal of attention to the role of the vestibular information. One explanation for this focus is the fact that the labyrinths of the inner ear provide information about the linear and angular displacements of the head relative to space and also of the body by combining vestibular and neck muscle proprioception inputs. For comparison, the visual inputs, in their preliminary stage of processing, are more ambiguous because a given change of retinal inputs can result from either self motion (i.e., head and/or body) or motion of the objects from the environment.

Psychophysical studies have indisputably demonstrated that one can process vestibular information to create a percept of self-motion in space. Among the most convincing demonstrations for the importance of vestibular output is the much larger motion perception threshold for both rotation directions after total bilateral vestibular ablation (Valko et al., 2012) or for rotations toward the lesion side after unilateral vestibular loss (Cousins et al., 2013). In addition, Fitzpatrick et al. (2002) reported that galvanic stimulation of the vestibular system (GVS) in neurologically intact individuals changes their perception of actual body rotations. These authors found that motion perception is enhanced when both the GVS and the rotation are congruent (i.e., when both stimuli activate and inhibit the same labyrinths' side) and is attenuated when both stimulations are incongruent.

The goal of the present study was to specifically assess the cognitive estimate of body displacement during the course of discrete body rotations. Previous investigations on motion perception during ongoing body displacements have essentially used protocols where subjects were asked to adjust the speed of a hand-steered lever according to the perceived rotation intensity (Guedry, 1974; Okada et al., 1999; Seemungal et al., 2007; Sinha et al., 2008; Bertolini et al., 2012; Shaikh et al., 2013) or to continuously point at a remote (unseen) target during body displacement (e.g., Loomis et al., 1992; Ivanenko et al., 1997a,b; Philbeck et al., 2001; Bresciani et al., 2005; Guillaud et al., 2006; Blouin et al., 2010;

Frissen et al., 2011). Because the former methods essentially test whether the subjects perceive the rotation as increasing, decreasing or constant, it does not provide information regarding the actual perception of angular displacement (Shaikh et al., 2013). On the other hand, with the latter methods (i.e., continuous pointing), one cannot determine the degree to which the responses provided by the subjects are issued from vestibular-issued sensorimomotor processes or from introspective estimation of body displacement. Indeed, experimental evidence was given that the compensatory arm movements leading to such hand stabilization derive from vestibulomotor transformations that involve negligible cognitive processes (Bresciani et al., 2005; Blouin et al., 2010). Moreover, the fact that the motor systems may have access to spatial information that may not be readily available to the perceptual system (Goodale and Milner, 1992; Prablanc and Martin, 1992; Milner and Goodale, 2008) also increases the uncertainty regarding the contribution of perceptual processes in stabilizing the hand during body motion. In the present study, participants were asked to indicate, by rotating the handle of a manipulandum mounted on a vertical axis (see **Figure 1**), their perceived change of angular position in space during passive body rotations. With this method, an unbiased response would be associated with rotating the manipulandum's handle in the same direction and amplitude as the actual body rotation.

When consulting the extant literature, the relatively good accuracy with which subjects perceive their passive motions could be viewed as odd considering the effects of these motions on the labyrinths during their deceleration phase. Indeed, the response of the vestibular receptors during motion deceleration in a given direction is similar to the response evoked when accelerating in the opposite direction. Based on these physiological characteristics of the vestibular system, one would expect individuals to perceive their displacements as being shorter during the deceleration compared to the acceleration, and therefore underestimate the magnitude of their total displacements. In fact, several studies have shown that subjects tend to underestimate their passive body displacement in darkness, when the absence of feedback on performance prevents any learning (i.e., Bloomberg et al., 1991; Israël, 1992; Israël et al., 1993b; Blouin et al., 1995a,b, 1997; Quarck et al., 2009; Simoneau et al., 2009; Vidal and Bülthoff, 2010). Moreover, marked underestimation of body displacement during deceleration has already been reported (Guillaud et al., 2006). In this latter study, subjects were required to maintain the orientation of their arm stretched horizontal during passive body rotations at different frequencies (from 0.05 to 0.34 Hz). The subjects produced accurate compensatory arm movements in both the acceleration and deceleration phases of the rotation when visual information was available. However, when the angular displacements could be detected only through somatosensory and vestibular cues issued during chair rotation (i.e., condition without vision), the online compensatory arm movements remained accurate during the acceleration, but largely underestimated the rotation during the deceleration. These underestimations suggested that the vestibular system provided underrated information of body rotation during deceleration. On the other hand, using a more cognitive task, Mackrous and Simoneau (2011) found evidence that participants overestimate their angular displacements during whole body rotation accelerations. In their study, participants were asked to press a push button when they felt that their body's midline had crossed a memorized target initially presented 60° in their



FIGURE 1 | Schematic representation of the experimental apparatus.

periphery. The participants usually pressed the button near the end of the acceleration while they were still far from the target (on average 16°). In the present study, the subjects' perception of body motion was assessed separately during the acceleration and deceleration phases of discrete body rotations to directly compare the cognitive estimate of body motion between these two phases.

MATERIALS AND METHODS

Thirteen healthy adults (six females, seven males; mean age 32 years) volunteered to participate to the study. Prior to their engagement in the experiment, participants were asked if they were aware of current or past existence of any history of vestibular or other neurological disorders. Only those individuals without such history of disorders were selected. The experiment was conducted with the understanding and written consent of each participant, in accordance with the ethical standards of Aix-Marseille University and those set out in the 1964 Declaration of Helsinki.

A schematic representation of the experimental set-up is shown in **Figure 1**. The participants were seated on a chair positioned above the axis of a revolving platform placed in the middle of a closed room (2.4 × 2.4 m). The lights of the room were turned off during the experiment leaving the participants in complete darkness. The participants were secured on the chair with a three-point safety belt. They wore audio earphones diffusing a white noise to mask possible auditory spatial reference cues. The use of a neck brace helped to restrict head-on-trunk displacement. The platform was rotated by a servomotor controlled by a Smart Motor Control Card (Baldor Electric Company). During rotation, participants were required to fixate a LED attached to the chair, positioned approximately 1 m in front of them. This procedure was used to minimize eye movements and to keep gaze direction similar across participants. This was judged important because it has been reported that different gaze direction may lead to different perception of rotations (Quarck et al., 2009). The participants' task was to report online the perceived rotation by rotating the manipulandum's handle. This handle was mounted on the axis of a potentiometer incorporated onto a small box positioned on the chair in front of them. The participants were told to rotate the handle by the same angular amplitude as the chair and in the same direction. They did not receive feedback about their performance during the experiment. Note that this method differs from the continuous pointing task in which participants must rotate the arm or pointer in the opposite direction of the rotations. Because vestibulomotor transformations are generally employed to stabilize the body and its segments (e.g., eyes, arm) during motion, movements of the handle in the present experimental task were more likely to arise from vestibular-issued cognitive processes than from more direct vestibulomotor processes. Rotations of the handle were measured with the potentiometer and the platform's angular position was returned to the computer by the axis control card. Signals sent to the chair, and received from the manipulandum and chair, were handled by a 12-bit analog/digital board (Keithley Instruments Inc.) installed in a real-time controller system (ADwin Pro, Jäger Computergesteuerte Messtechnik), which was programmed using custom-designed software (Docometre). The manipulandum potentiometer input was sampled at 500 Hz. During data reduction, both the handle and chair position signals were filtered using a zero-phase low-pass digital filter set at 10 Hz. Eye movements were monitored (but not recorded) to ensure that participants fixated the LED in front of them during the trials. To do so, we used a pair of goggles with a custom video-oculography unit (not represented in **Figure 1**) placed in front of the non-dominant, left eye (determined by the hole-in-card test; Miles, 1930). During the trials, the experimenter verified whether participants complied with the instruction regarding fixation of the chair-fixed LED. No trials had to be rejected based on non-compliance with this instruction.

The chair rotations were sinusoid-type angular velocity profiles, which had similar peak amplitude of 57°/s but varied in rise times (**Figure 2**). Acceleration duration (i.e., time to peak velocity) and deceleration duration (i.e., time between peak velocity and rotation offset) were either 1.5 or 3 s. High acceleration or deceleration (AccHigh; DecHigh) will refer to those that lasted 1.5 s (peak of 60°/s^2) and low acceleration or deceleration (AccLow; DecLow) to those lasting 3 s (peak of 33°/s^2). All combinations of acceleration and deceleration ($N = 4$) were used for both clockwise and counter-clockwise rotations. Depending on the acceleration and deceleration combination, the participants could be rotated by 110° (**Figure 2D**), 165° (**Figures 2B,C**) or 220° (**Figure 2A**). We used different combinations of acceleration and deceleration in order to diminish the participants' possibility to predict the deceleration on the basis of the previous acceleration. By doing so, it was also possible to test whether changing acceleration and deceleration intensities had an effect of the participants' perception of their rotations. The position reached by the chair at the end of the trials was used as the starting position of the next trial. At least 25 s separated each trial. Eight trials were run per condition and the different conditions were randomly presented.

Figure 3 shows one example of the angular displacements and velocities of the chair and manipulandum's handle (i.e., participant's response). As depicted, the angular displacements of the handle increased relatively smoothly during the rotation. Clearly however, the velocity of the handle and of the chair motions did not match (compare velocity traces of **Figure 3**). The fact that the participants were instructed to reproduce their perceived angular displacements rather then the velocity of their rotations could explain the large discrepancy between the chair and handle velocity measurements (note that the velocity reproduction was also less reliable than in continuous pointing tasks, e.g., Ivanenko et al., 1997a; Guillaud et al., 2006). To assess participants' perception of rotations, we computed the ratio between the amplitude of the perceived rotations (as measured by the rotating handle) and the amplitude of the actual chair rotations. This ratio, hereafter referred to as the gain, was measured at the end of the rotations (total gain), and was also computed separately for the acceleration and deceleration phases. Unless otherwise specified, the computed gains were analyzed using separate ANOVAs. First, the effects of the phase, intensity and direction were specifically tested using a 2 (Phase:

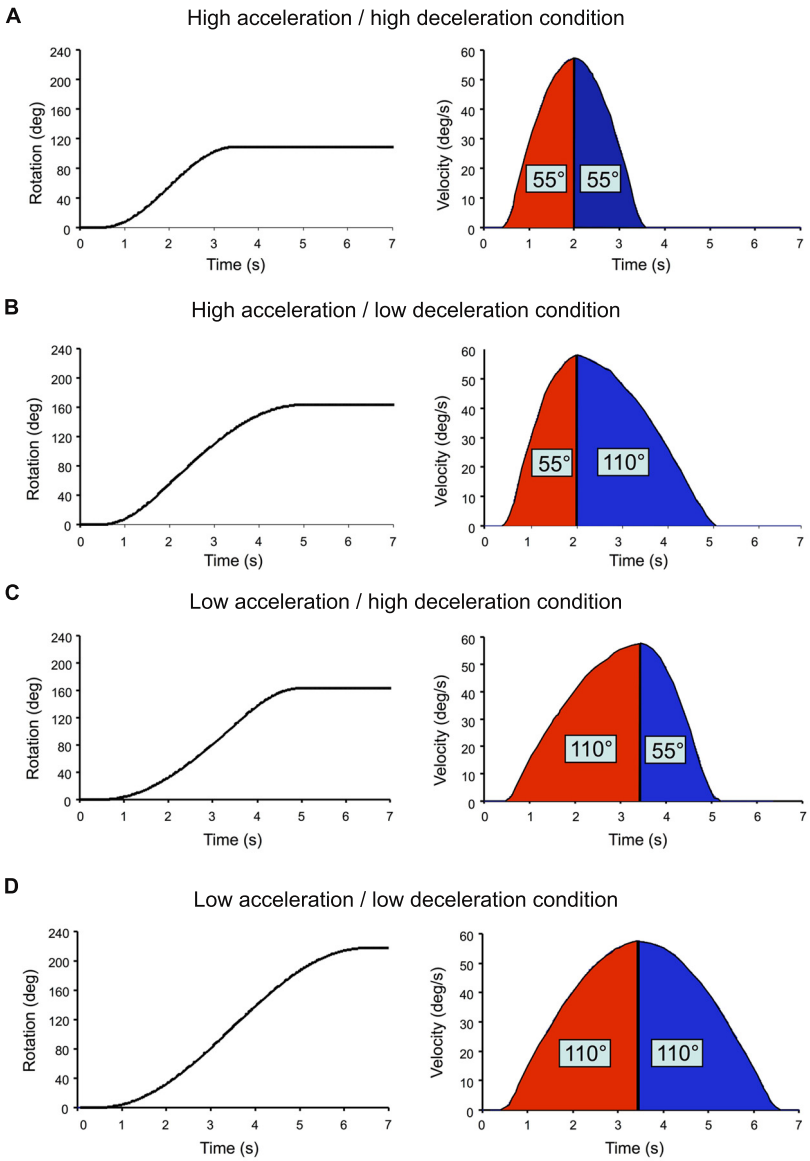


FIGURE 2 | Angular displacement (returned to the computer by the axis control card) and velocity (computed offline) of the chair in each tested combination of acceleration and deceleration. Rotation onset occurred 500 ms after the onset of the recordings. **(A)** High acceleration/high deceleration condition; **(B)** high acceleration/low deceleration condition; **(C)** low acceleration/high deceleration condition; **(D)** low acceleration/low deceleration condition.

acceleration, deceleration) × 2 (Intensity: low, high) × 2 (Direction: counter-clockwise, clockwise) repeated measures ANOVAs. Then, the gain measured at the end of the rotation (total gain) was submitted to a 4 (Profile: AccLow-DecLow; AccLow-DecHigh; AccHigh-DecLow; AccHigh-DecHigh) × 2 (Direction: counter-clockwise, clockwise) repeated measures ANOVA. The same analyzes were also performed on the variability of the gains (i.e., intra-subject standard deviation of the mean). The statistical threshold was set to $p < 0.05$ for all statistical analyzes and significant effects were further analyzed using Newman–Keuls tests. All significant effects and interactions are reported.

RESULTS

The participants' perception of their passive displacements markedly differed between the acceleration and deceleration phases of the rotation and was also dependent on the intensity of these phases (see **Figure 4**). The effects of the independent variables on the gain were confirmed by the 2 (Phase) × 2 (Intensity) × 2 (Direction) ANOVA which revealed a significant main effect of Phase ($F(1,12) = 50.83$, $p < 0.001$) and a significant Phase × Intensity interaction ($F(1,12) = 8.18$, $p < 0.01$). On average, the gain was markedly greater during the acceleration (mean = 1.19) than during the deceleration (mean = 0.67). The breakdown of the interaction revealed that the factor Intensity

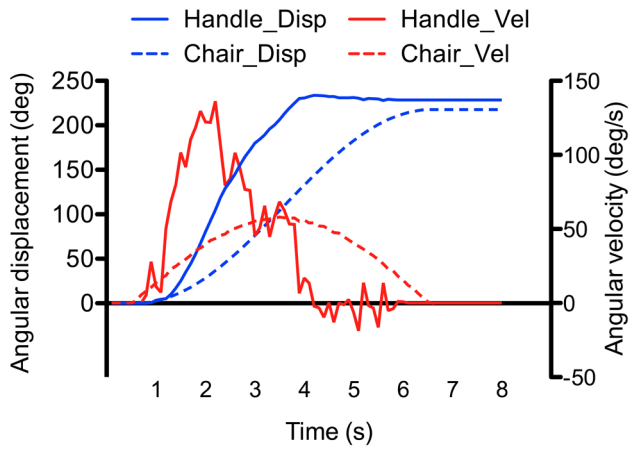


FIGURE 3 | Example of recorded angular displacement and velocity of the chair and manipulandumss handle (the example was taken from the AccLow-DecLow condition which rotated the participant by 220°).

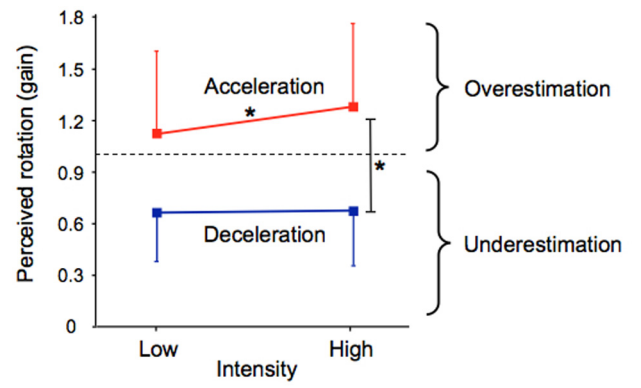


FIGURE 4 | Mean acceleration and deceleration gains as a function of their intensity. The vertical bars represent between-subjects standard deviations. *$p < 0.01$.

had a significant effect only during the acceleration, the gain being greater in the high (mean = 1.28) than in the low (mean = 1.11) intensity. As shown by the size of the vertical bars in **Figure 4**, the gain computed in the different phases of the rotation considerably varied between the participants.

The same 2 × 2 × 2 ANOVA performed on the intra-subject variability revealed significant effects of Phase ($F(1,12) = 15.56$, $p < 0.01$) and Intensity ($F(1,12) = 33.54$, $p < 0.001$; not illustrated). Participants showed greater variability in perceiving their rotation during the acceleration phase (mean = 0.23) than during the deceleration phase (mean = 0.17). High intensity rotational stimuli (mean = 0.23) also resulted in greater variability compared to low intensity (mean = 0.17). Therefore, the greater mean gains were associated with the greater intra-subject variability.

Results reported above showed considerable inter-participant variability in the perception of self-motion, irrespectively of the considered phase and intensity of the rotation. To determine whether the effect of Phase (i.e., greater gain in acceleration than in deceleration) was consistent across participants, we subtracted the deceleration's gain from the acceleration's gain, for each type of velocity profile (averaged for counter-clockwise and clockwise rotations) and each participant. Positive differences resulting from this computation would indicate greater gain in the acceleration than in the deceleration. As shown by **Figure 5**, the differences between the gains of both rotation phases considerably varied between participants. But more importantly, only positive differences resulted from this computation, which indicates that the gain was greater in the acceleration than in the deceleration for all participants and for all combinations of acceleration and deceleration. It is worth noting that participants' rotatory response may have lagged the chair rotation due to delays in sensorimotor systems and to the time required to cognitively process the vestibular input (see Barnett-Cowan, 2013 for a review). As such, because we measured acceleration gain at the end of the acceleration without correcting for a possible lag, it must be noted that the high acceleration gain computed here, which supports Mackrous and Simoneau's (2011) findings, could actually underestimate the actual participants' perception of their displacement during that phase.

As detailed above and illustrated in **Figure 4**, deceleration intensity had no significant effect on the participants' perception of their rotation during that phase. We performed an additional analysis to specifically test whether the participants' perception during the deceleration was influenced by the intensity of the preceding acceleration. To this end, we plotted the deceleration gain as a function of the acceleration gain for all participants and then computed the linear regression for each rotational stimulus (combining counter-clockwise and clockwise rotations). Our reasoning was as follows: if the intensity of the acceleration has an effect on the perception of rotation during the deceleration, then the slope of the linear regression should differ between the conditions with different acceleration intensities. The results of these regression analyzes are shown in **Figure 6**. In all conditions, the slope of the regression line was much smaller than 1, corroborating our previous analyzes showing that the gain during the deceleration

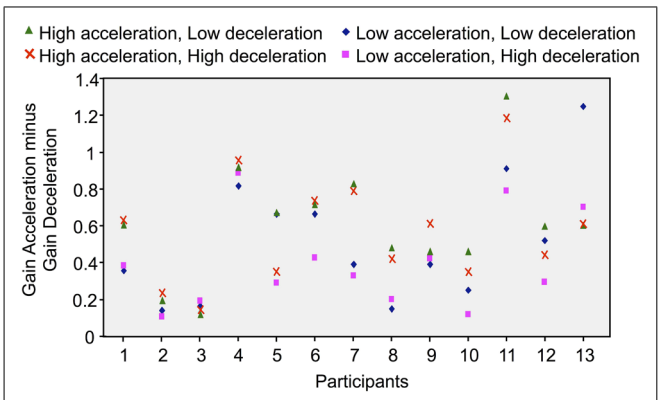


FIGURE 5 | Difference between the acceleration and deceleration gains computed in each rotational stimulus and for each participant (the positive values indicate that the gains were greater in the acceleration than in the deceleration).

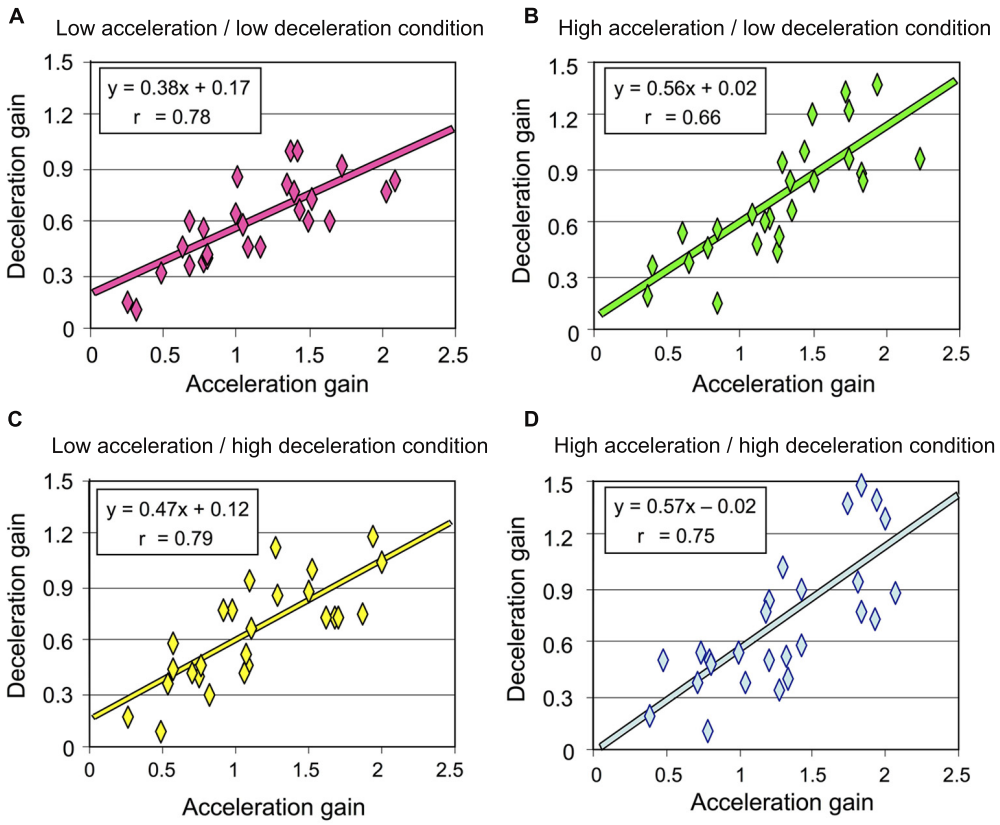


FIGURE 6 | Deceleration gain of all participants plotted against the acceleration in each rotational stimulus (combining counter-clockwise and clockwise rotations) (A) Low acceleration/low deceleration condition; **(B)** high acceleration/low deceleration condition; **(C)** low acceleration/high deceleration condition; **(D)** high acceleration/high deceleration condition.

was smaller than during the acceleration. However, the regressions computed in both conditions with high acceleration were characterized with larger slopes (mean 0.565, **Figures 6B,D**) than those computed in both conditions with low acceleration (mean 0.425, **Figures 6A,C**). Therefore, the greater was the acceleration, the greater was the perceived displacement during the deceleration. These results then suggest that the intensity of the angular acceleration influenced the participants' perception of rotation during the subsequent decelerating phase.

The participants' perception of their total passive displacements also depended on the acceleration and deceleration with which they were rotated. The mean total gain (i.e., computed at the end of the rotation) was greatest in the AccHigh-DecHigh condition (mean = 0.99) and smallest in the AccLow-DecLow condition (mean = 0.85). The ANOVA performed on this gain revealed a significant effect of Profile ($F(3,36) = 8.94$, $p < 0.001$). As illustrated in **Figure 7** and confirmed by *post hoc* analyzes, the total gain in the AccHigh-DecHigh condition was significantly greater than in both the AccHigh-DecLow and AccLow-DecLow conditions and it was greater in the AccLow-DecHigh condition than in the AccLow-DecLow condition. The total gain considerably varied between the participants. This large variability is evident in **Figure 7** in which the errors bars represent between-subjects standard deviations, which ranged between 0.34 and 0.40 across conditions.

The ANOVA performed on the intra-subject variability of the total gain (not illustrated) also revealed a significant effect of Profile ($F(3,36) = 3.78$, $p < 0.05$). *Post hoc* analyzes showed that this variability was greater in the AccHigh-DecHigh condition (mean = 0.17) than in the AccLow-DecLow condition (mean = 0.11). Intra-subject variability was therefore greater in the condition with the greatest total mean gain than in the condition with the smallest total mean gain.

DISCUSSION

The results of the present study showed that the perception of self-motion greatly varies during the course of discrete body rotations. Indeed, we found that the participants' estimates of their angular displacement were markedly larger during the acceleration phase of the rotation than during the deceleration phase. This was true even in conditions where the deceleration was the inverse mirror image of the acceleration, i.e., when the dynamics of the angular motion and the distance covered by the participants were similar in both phases.

In this study, we used a protocol that maximized the need of processing vestibular information online by asking the

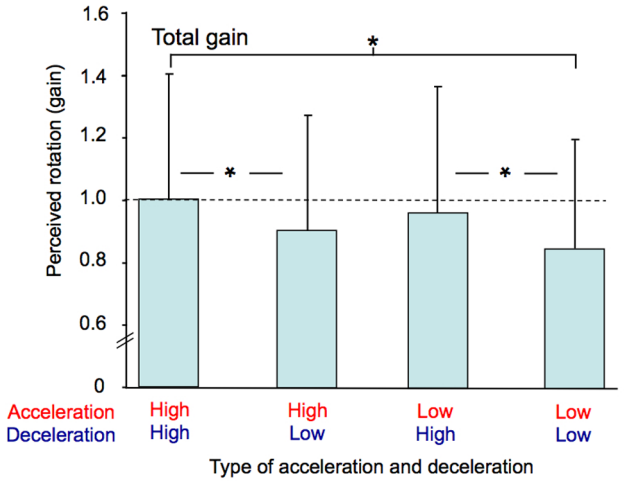


FIGURE 7 | Mean total gain computed for each combination of acceleration and deceleration (averaged for both counter-clockwise and clockwise rotations). The vertical bars represent between-subjects standard deviations and the dotted line indicates a gain of one. * $p < 0.01$.

participants to report their perceived body angular displacements in real-time and making a random use of symmetric and asymmetric acceleration-deceleration profiles, which had different magnitudes and directions. This important aspect of the present study rendered predictive mechanisms inefficient to determine the actual body displacement. Prediction of motion, which is enhanced during symmetric acceleration-deceleration, is known to benefit to the online control of manual and ocular tracking of targets moving with such profiles (Poulton, 1981; Bahill and McDonald, 1983; Vercher and Gauthier, 1992; Xia and Barnes, 1999). With symmetric kinematic profiles, predictive mechanisms could particularly affect motion perception during deceleration, because the dynamics of the deceleration could be inferred from the dynamics of the acceleration.

Despite our methodological precaution of trial randomization, we cannot fully exclude a possible contribution of predictive mechanisms. Nevertheless, the regression lines computed after plotting the acceleration and deceleration gains can help to argue that in the context of the present experiment, acceleration-based prediction of body rotation during the deceleration may have been limited, at least in conditions with high acceleration. Before going into more detail, it appears useful to recall two important methodological aspects of the present experiment: (i) the gains reported here were measured using angular displacement data recorded from both the chair and the manipulandum (the latter being thought to reflect the participants' perception of their own motion) and (ii) the chair angular displacement was smaller during high acceleration or deceleration (i.e., 55°) than during low acceleration or deceleration (i.e., 110°). Presumably, if the perceived deceleration were to be based on acceleration-derived prediction mechanisms, the slope of the regression line should have been smaller in the high acceleration/low deceleration condition than in the high acceleration/high deceleration condition. Indeed, predicting a 55° rotation during the deceleration in the former condition would have largely decreased the gain measured during the 110° deceleration. However, we found that the slopes computed in these conditions, which had similar acceleration (i.e., high) but different deceleration intensities were remarkably alike (compare **Figures 6B,D**) thus suggesting small impact of predictive mechanisms in the perception of body rotation during deceleration.

However, body acceleration may have affected the participants' perception of self-motion during deceleration in a somewhat more indirect way, and that is, through the so-called velocity storage mechanism. Indeed, the brain is believed to be equipped with neural integrators that allow prolonging vestibular signals and therefore sensation of rotation, which cannot be explained on the sole basis of the labyrinths' output (Raphan et al., 1979). For instance, this central process is thought to be responsible for the fact that participants perceive their angular velocity as increasing when it actually reaches a plateau (Brown, 1966; Sinha et al., 2008; Shaikh et al., 2013). These observations raise the question of the role that might play the accumulation of these neural integrators (velocity storage) during body acceleration in the perception of self-displacement during deceleration. In the present study, participants perceived greater rotation during the deceleration when the preceding acceleration was greater (66 vs. 30°/s^2) and shorter (1.5 vs. 3 s). This was observed for both deceleration intensities (i.e., low, high). While the present psychophysical experiment does not allow one to make decisive claims regarding the neural mechanisms responsible for this finding, it appears reasonable to speculate greater velocity storage in the condition with greater angular acceleration, increasing the perceived angular displacement during their following deceleration.

To some extent, both the smaller gain observed in conditions with longer acceleration and the underestimation of the rotation observed during body deceleration could be linked to the effect of the turning stimuli on the relative motion between the endolymph and the semicircular canals. For instance, during clockwise head angular acceleration, due to the inertia of the endolymph, the hair bundles bend toward the kinocilium of the right labyrinth and away from the kinocilium of the left labyrinth. This leads to an increase and decrease discharge rate of the right and left vestibular afferent fibres, respectively (hence indicating clockwise head motion; Goldberg and Fernandez, 1971). Rapidly however, due to friction with the canals' inner walls, the velocity of the endolymph approaches that of the head (Dodge, 1923; Goldberg and Fernandez, 1971; Laurens and Angelaki, 2011). It turns out that the rotation-related vestibular output decreases as the duration of the acceleration increases. In the present experiment, this phenomenon could explain the smaller gain observed when the acceleration lasted 3 s compared to 1.5 s.

Moreover, because the endolymph is moving in space during prolonged acceleration, during head deceleration, motion of the endolymph (again because of its inertia) becomes greater than that of the head and of the hair bundles. This causes the endolymph to push the hair bundles in the opposite direction than at the onset of head rotation, even though the head is still rotating (i.e., decelerating) in the same direction. This phenomenon is responsible for the perception of body rotation in the opposite direction to the actual rotation, when the deceleration occurs after prolonged

rotation at constant velocity (e.g., Bockisch and Haslwanter, 1997; St George et al., 2011). In our experiment, this phenomenon, even if it could have been compensated for to some extent by velocity-storage mechanisms, could have contributed to the weakened sense of rotation during the deceleration.

The different perception of body rotations during the acceleration and deceleration phases could also be linked to the different effects of these phases on time perception, as reported in several papers (e.g., Israël et al., 2004; Capelli and Israël, 2007; Binetti et al., 2010, 2013). These studies showed that one perceives the time as being faster during body acceleration and as being shorter during deceleration. Based on these findings, suggestion has been made that vestibular stimulation could increase the rhythm of internal clock pacemaker during acceleration and decrease it during deceleration. Therefore, accelerating and decelerating the body would not strictly differently affect vestibular-mediated actions (as evidenced here and in Guillaud et al.'s (2006) study) but would also impact non-spatial cognitive processes. In all cases, the reported observations could suggest increased and decreased states of arousal during acceleration and deceleration, respectively. This would be compatible with the idea that attentional resources are required to accurately monitor changes in body orientation through vestibular inputs (Yardley et al., 1999) and that arousal increases the speed of the internal pacemaker (Burle and Casini, 2001). In this framework, it is possible that the participants' attentional level was greater at the beginning of the rotations, i.e., during the acceleration (and more particularly during the short acceleration where we found greater gain), than afterward during the deceleration. Note that other studies have revealed significant impact of vestibular stimulations on not explicitly spatial cognitive processes (e.g. bodily awareness and number generation; Lopez et al., 2010; Ferrè et al., 2013a,b).

Lastly, we found large intra- and inter-individual variability in the perception of body rotation. This phenomenon was observed irrespectively of the considered rotation phase (i.e., acceleration, deceleration, total rotation). One possible explanation for this observation is the use of linear acceleration profile of body rotation, which is known to be associated with larger inter- and intra-subject variability than step acceleration (i.e., sharp and short acceleration that is followed by a constant acceleration, Gianna et al., 1996). The large variabilities observed here may also reflect the difficulty of the perceptual system to have access to continuous positional information from velocity-related vestibular input. In the present experiment, participants were asked to reproduce online their perceived angular displacement rather than the velocity of the rotation. Because the semi-circular canals respond to angular acceleration, a double integration is needed to estimate body orientation during rotations. A first peripheral integration is carried out within the vestibular apparatus itself and the second is carried out in the central nervous system (Robinson, 1989; McFarland and Fuchs, 1992). When performed offline and with less time constraints than in our task (i.e., after body motion), such transformation of vestibular cues into position cues appears less noisy (e.g., when estimating the position held before being passively moved, Bloomberg et al., 1988; Israël, 1992; Israël et al., 1993a, 1999; Blouin et al., 1995a,b 1997). This may also suggest that the more accurate and less variable hand or arm responses reported in continuous pointing tasks studies – when moving participants point toward a memorized Earth-fixed object (see introduction) – were essentially based upon vestibular-issued velocity cues rather than positional cues.

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AUTHOR CONTRIBUTIONS

Luc Tremblay, Liliane Borel, Laurence Mouchnino, and Jean Blouin conceived the study. Dany Paleressompoulle built the apparatus. Luc Tremblay and Andrew Kennedy performed the data acquisition. Luc Tremblay, Andrew Kennedy, and Jean Blouin analyzed the data. Luc Tremblay, Liliane Borel, Laurence Mouchnino, and Jean Blouin evaluated the data. Luc Tremblay and Jean Blouin wrote the manuscript. Liliane Borel and Laurence Mouchnino improved the manuscript.

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Vestibular function in the temporal and parietal cortex: distinct velocity and inertial processing pathways

Jocelyne Ventre-Dominey*

INSERM U846, Stem Cell and Brain Research Institute, Lyon University, Bron, France

Edited by:
Stephane Besnard, INSERM U1075, France

Reviewed by:
Barry M. Seemungal, Imperial College London, UK
Martin Hitier, INSERM U1075, France

****Correspondence:***
Jocelyne Ventre-Dominey, INSERM U846, Stem Cell and Brain Research Institute, Lyon University, 18 Avenue Doyen Lepine, Bron 69500, France
e-mail: jocelyne.ventre-dominey@inserm.fr

A number of behavioral and neuroimaging studies have reported converging data in favor of a cortical network for vestibular function, distributed between the temporo-parietal cortex and the prefrontal cortex in the primate. In this review, we focus on the role of the cerebral cortex in visuo-vestibular integration including the motion sensitive temporo-occipital areas i.e., the middle superior temporal area (MST) and the parietal cortex. Indeed, these two neighboring cortical regions, though they both receive combined vestibular and visual information, have distinct implications in vestibular function. In sum, this review of the literature leads to the idea of two separate cortical vestibular sub-systems forming (1) a velocity pathway including MST and direct descending pathways on vestibular nuclei. As it receives well-defined visual and vestibular velocity signals, this pathway is likely involved in heading perception and rapid top-down regulation of eye/head coordination and (2) an inertial processing pathway involving the parietal cortex in connection with the subcortical vestibular nuclei complex responsible for velocity storage integration. This vestibular cortical pathway would be implicated in high-order multimodal integration and cognitive functions, including world space and self-referential processing.

Keywords: vestibular, parieto-temporal cortex, MST, spatial representation, self-referential, egomotion

INTRODUCTION

Since the early clinical observations suggestive of a cortical role in vestibular function (Carmichael et al., 1954; Penfield and Jasper, 1954), empirical data on the underpinnings of such a cortical vestibular integration have been provided only in the 1980s, by behavioral and electrophysiological recording experiments conducted in animals. Thus, by neural unit recordings, discharges of neurons located in the visual associative cortex were observed during body rotations in cat (Becker et al., 1979; Deecke et al., 1979; Mergner, 1979; Vanni-Mercier and Magnin, 1982a,b) and in monkey (Kawano et al., 1980, 1984; Kawano and Sasaki, 1984; Akbarian et al., 1988; Grusser et al., 1990a,b). More precisely, visual tracking neurons were found in monkey to receive vestibular information in cortical sites located in the associative parietal and temporal cortex (Kawano et al., 1980, 1984; Kawano and Sasaki, 1984) and in the retro-insular cortex (Grusser et al., 1990a,b). In our early work studying effects of cortical lesions in the cat (Ventre, 1985a,b), we described a parcellation of visuo-vestibular areas distributed in the suprasylvian (SS) cortex divided into two regions: the middle SS gyrus (area 7) preferentially involved in vestibularly driven ocular responses and the lateral SS sulcus implicated in optokinetic ocular responses. Similarly, a pattern of visual extrastriate areas localized in the superior temporal sulcus in monkey and described as MT (middle temporal) and MST (middle superior temporal) areas were found to be activated during visual motion as well as during visuo-vestibular interactions (Komatsu and Wurtz, 1988a,b; Newsome et al., 1988), thereby suggesting in primate similar visual and vestibular cortical organization as in the cat (Tusa et al., 1989; Ventre, 1985a,b). Indeed, based on recent data on neuronal receptive field properties and visual behavior (Lomber and Payne, 2004), this lateral suprasylvian sulcus (area PMLS) is equated to the visual areas located in the middle temporal sulcus in macaque monkey.

By combining lesions and tracer injections (Ventre and Faugier-Grimaud, 1986, 1989; Faugier-Grimaud and Ventre, 1989) or electrophysiology and tracer injections (Akbarian et al., 1994, 1993) evidence has been provided in monkey of a larger vestibular network distributed between the parieto-temporal cortex, the retro-insular and the prefrontal cortex and directly connected to the vestibular nuclei complex. Only recently, over the last two decades, the advanced neuroimaging techniques have given access to the investigation of human brain activation elicited during either caloric ear irrigation or galvanic vestibular stimulation (Bottini et al., 1994, 2001; Bucher et al., 1997; Vitte et al., 1996; Lobel et al., 1998; Fasold et al., 2002; Dieterich et al., 2003; Emri et al., 2003; Naito et al., 2003; Stephan et al., 2005; Eickhoff et al., 2006; Lopez et al., 2012; Zu Eulenburg et al., 2012). These authors demonstrated in healthy subjects that such vestibular stimulations triggered activity in distributed cortical areas including the posterior temporo-parietal and retro-insular cortex, the intraparietal sulcus (homologue to area 2v), the somatosensory area 3 as well as rostrally several frontal regions (middle and inferior frontal gyri) and the anterior cingulate cortex. Interestingly, there is a striking homology between the vestibular cortical networks described in monkey and in man (see for review,Fukushima, 1997; Brandt and Dieterich, 1999; Lopez and Blanke, 2011). **Figure 1** illustrates the inter-species organization and growing complexity of the vestibular cortical fields. While convincing evidence is now provided for a link between vestibular function and cortical processes, the

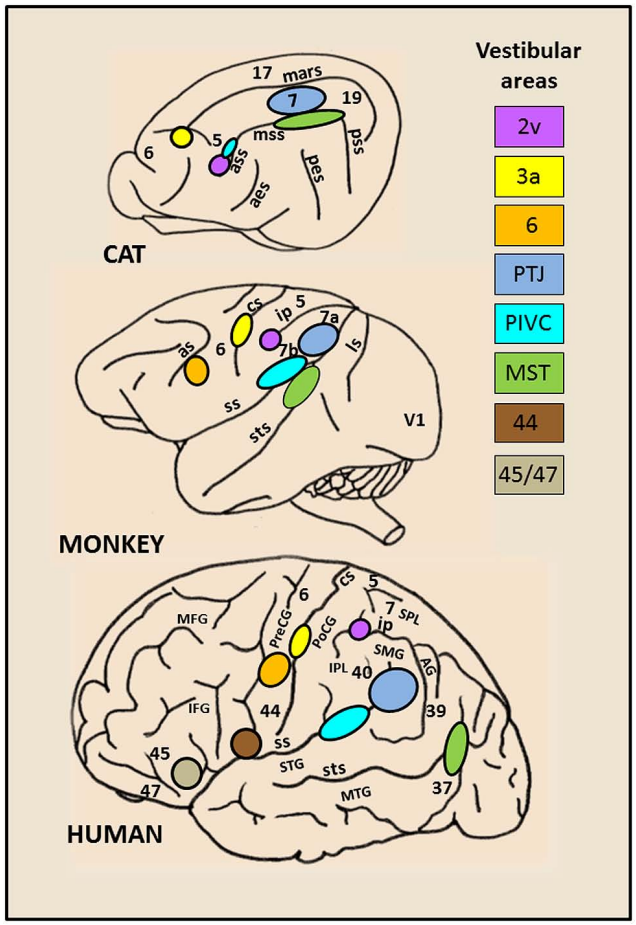


FIGURE 1 | Schematic brain representations illustrating the topography of the vestibular cortical fields as they have been experimentally identified in cat, monkey, and human. The numbers on the cortex indicate the architectonically defined Brodman's areas (based on (Talairach and Tournoux, 1988). In the right panel are listed the vestibular sites with their localization in the cortical regions. In cat: the marginal sulcus (mars), the anterior (ass), middle (mss) and posterior (pss) suprasylvian sulci, the anterior (aes) and posterior (pes) ectosylvian sulci. In primate (monkey and human): the lunate sulcus (ls), the superior temporal sulcus (sts), the sylvian scissure (ss), the intraparietal sulcus (ip), the central sulcus (cs) and the arcuate sulcus (as), the superior (STS) and middle (MTG) temporal gyri, the angular gyrus (AG), the supramarginal gyrus (SMG), the superior (SPL) and inferior (IPL) parietal lobes, the postcentral (PoCG) and precentral (PreCG) gyri, the middle (MFG) and inferior (IFG) frontal gyri.

exact roles of these various cortical sites topographically similar in animal and human, remain obscure. Recent studies suggest a role of some of these cortical vestibular sites in cognitive processes relying on vestibular integration i.e. spatial representation and self-consciousness (see for review, Lopez and Blanke, 2011).

On the basis of the subcortical organization of the vestibular function largely described in the past (Robinson, 1977; Raphan et al., 1979; Cohen et al., 1981; Raphan and Cohen, 1985), the vestibulo-ocular responses rely on two cooperating kinematic processes: (1) the direct process is responsible for the gain of the ocular responses that will trigger ocular responses to rapidly compensate for head motion and (2) the indirect process is responsible for a low-frequency kinematic component insuring a multimodal integration of the vestibular signals for the purpose of storage and updating of spatial coordinates (Wearne et al., 1997, 1998; Cohen et al., 1999; Raphan and Cohen, 2002; Leigh, 2006). Such a dual path organization of the vestibular system is also reflected in vestibular evoked control of goal-directed arm movements (Bresciani et al., 2002, 2005).

In the following review of the literature, we will attempt to draw a parallel between such a dual organization of the vestibular function as demonstrated in subcortical regions, and the organization of the temporo- parietal cortex. Thus, we hypothesize that the cortical integration of vestibular information is organized as a twofold system of pathways originating from the temporal and parietal cortices which respectively mediate vestibularly driven velocity and inertial signals. As the cortical properties have been extensively investigated in human and non-human primate, we will mainly refer in the following to the studies describing the cortical processes linked to ego-motion in these species. However, the inter-species similarities described above demonstrate the functional coherence and evolutionary continuity that emphasize the physiological foundations for visual and vestibular interactions in the cerebral cortex especially in the parietal and temporal lobes.

IS THE TEMPORAL CORTEX INVOLVED IN A VELOCITY PATHWAY?

A perceived displacement of the visual surroundings can be triggered by the retinal slip of the visual environment or by head/body motion. In order to differentiate between the motion of the visual surrounding versus self-motion, the central nervous system must integrate multimodal signals including visual and vestibular signals in order to extract the origin and direction of the perceived movement. As mentioned above, cortical visual and vestibular interaction has been first suggested in the visual lateral suprasylvian cortex in cat (Vanni-Mercier and Magnin, 1982a,b; Ventre, 1985a,b; Rauschecker et al., 1987; Tusa et al., 1989) and in the middle temporal sulcus in macaque monkey (Dursteler and Wurtz, 1988; Komatsu and Wurtz, 1988a,b). These visual temporal cortical areas called MT (middle temporal) and MST (middle superior temporal) have a critical role in visual motion processes linked to smooth pursuit, heading perception and optokinetic-related information, all involving velocity signals triggered during ego-motion in monkey. In the following, we will see how the visual and vestibular signals are processed in the temporal cortex (MST) to provide velocity information about ego-motion. The main findings leading to the idea of a velocity pathway in the temporal cortical region will be developed in the two next sections successively for the integration of visual (visual motion) and vestibular (body motion) kinetic inputs.

VISUAL COMPONENT OF SELF-MOTION ANALYSIS

Monkey extrastriate visual areas including MT and MST have been largely investigated first in visual motion processing (Zeki, 1974; Maunsell and Van Essen, 1983; Newsome et al., 1985; Desimone and Ungerleider, 1986). Their majority of cells responsive

to moving visual stimuli is linked to smooth pursuit (SP) in a preferred direction but differed in the size of their receptive fields, with MST having larger receptive fields (Zeki, 1974; Komatsu and Wurtz, 1988a,b, 1989). These extrastriate visual areas have been first described for their role in pursuit and compensatory eye movement generation due to visual field displacements and more recently they have been implicated in self-motion and heading perception. In the context of self-motion, the most interesting units are in MST, the pursuit cells preferentially activated during moving background (Erickson and Dow, 1989; Inaba et al., 2007). Such pursuit cells have opposite preferred direction for pursuit and visual motion leading to a synergistic response during pursuit in the light (Erickson and Dow, 1989). Interestingly as suggested by Komatsu and Wurtz (1988b), such a synergistic response of MST neurons might be to increase the pursuit response of these cells to compensate for the optokinetic nystagmus. Even though suggested by these electrophysiological works in monkey, the idea of a role of MST in visuo-vestibular function in the primate will only clearly emerge from focal lesions studies. Thus, Dursteler and Wurtz (1988) demonstrated that chemical lesions in MST can induce twofold deficits in optokinetic nystagmus (OKN) (1) a reduction in the slow OKN build-up related to a directional pursuit deficit toward the lesioned side and (2) a reduction in the fast OKN build-up related to a retinal deficit with no specific directional preponderance. In accordance with our own observations in the cat (Ventre, 1985a,b), these findings were the first demonstration in monkey of the contribution of extrastriate cortex, including MST on OKN generation. In humans, OKN deficits described with a reduction of ipsiversive slow phase velocity have been reported first in large cortical lesions, including parietal cortex (Carmichael et al., 1954; Smith and Cogan, 1959) and in a subset of extrastriate cortical areas near the temporo-parieto-occipital region (Thurston et al., 1988; Morrow and Sharpe, 1990; Barton et al., 1996; Heide et al., 1996, Lekwuwa and Barnes, 1996). Taken together, these observations argue in favor of a role of MST area in computation of velocity signals issued from moving surrounding objects and used to produce pursuit and compensatory eye movements like OKN.

This MST activity in computing velocity signals of visual motion can give rise to perception of self-displacements. By studying the effects of optic flow on the activity of MST neurons, evidence has been provided in monkey of a role in heading perception of this visual area (Page and Duffy, 1999; Shenoy et al., 1999; Gu et al., 2006, 2010, 2012; Fetsch et al., 2010). Indeed, MST neurons are tuned to structured visual patterns in movement either in the fronto-parallell, radial, or expansion/contraction directions (Tanaka and Saito, 1989; Tanaka et al., 1989; Graziano et al., 1994; Fetsch et al., 2007). **Figure 2** shows an example of MST cells discharging to simple and distorted flow fields that simulate self-motion plus an eye movement (Bremmer et al., 2010). Bremmer et al. (2010) demonstrate that these MST neurons are able to compensate for visual distortion and to maintain their tuning response to the visual flow direction corresponding to heading information.

It is likely that MST yields a common cortical process subserving heading perception and optokinetic response generation, both elicited by large visual field displacements. Recent works (Cardin and Smith, 2011) suggest that a subset of cortical regions, including MST, the ventral intraparietal area, the medial visual area V6 as well as the cingulate cortex could integrate stereoscopic visual cues into ego-motion information. Neuroimaging using PET or fMRI approaches have demonstrated that human occipito-temporal cortex is engaged in the processing of retinal and extraretinal SP velocity as well as optokinetic signals (Barton et al., 1996; Bucher et al., 1997; Freitag et al., 1998; Petit and Haxby, 1999; Nagel et al., 2008). In sum, MST neurons might contribute to distinguish between external versus self-induced motion. However, such a computation requires that the visual signals about the environment displacement and the vestibular signals about the body motion are integrated in this same cortical region. The next section will show how combined with the visual signals, the vestibular signals about body motion will disambiguate ego-motion from object motion.

VESTIBULAR COMPONENT OF SELF-MOTION ANALYSIS

As previously mentioned, extrastriate visual areas including MST, the medial area V6 and VIP, might participate in the encoding of combined retinal and extraretinal signals including vestibular signals related to head displacements. The most thoroughly investigated is the dorsal part of MST (MSTd) in monkey (Page and Duffy, 1999; Gu et al., 2006, 2010, 2012; Fetsch et al., 2010). Recently a series of electrophysiological experiments in monkey clearly demonstrate that these MSTd neurons were firing during optic flow as well as during vestibular stimulation, hence subtending heading perception in separate reference frames, respectively eye-centered and head-centered (Fetsch et al., 2007; Gu et al., 2007, 2012, Takahashi et al., 2007). In the context of self-motion perception, the notion of an integration of vestibular signals in this extrastriate cortex then follows logically, and is clearly demonstrated via unit recordings in monkey after bilateral labyrinthectomy (Takahashi et al., 2007). In bilaterally labyrinthectomized animals, the MSTd neurons' firing rate is significantly diminished for physical rotation and translation in the dark, and not in the visual condition. Takahashi et al. (2007) suggested that the vestibular signals in MSTd could compensate for the ambiguous effects of the optic flow information during head movements. Indeed, as illustrated in **Figure 3**, many neurons in MSTd respond during vestibular stimulation in the dark and can display the same or opposite tuning for direction of motion in both visual and vestibular modalities, suggesting multimodal interactions in encoding heading (Bremmer et al., 1999; Gu et al., 2006; Fetsch et al., 2007, 2010). Based on these findings, it is likely that the extrastriate visual area MST contributes to self-motion regulation in coupling visual and vestibular kinetic information in order to compensate for retinal slip and thereby to maintain world stability during ego-motion. If evidence is provided of such MST influence on self-motion, it is not exclusive as visual and vestibular heading encoding has also been found in macaque ventral intraparietal area (VIP; Bremmer et al., 2002; Schlack et al., 2002; Klam and Graf, 2003). However, even though VIP neurons' discharges have similar selectivity as MSTd, VIP might be more specialized in the detection of targets approaching the face (Colby et al., 1993).

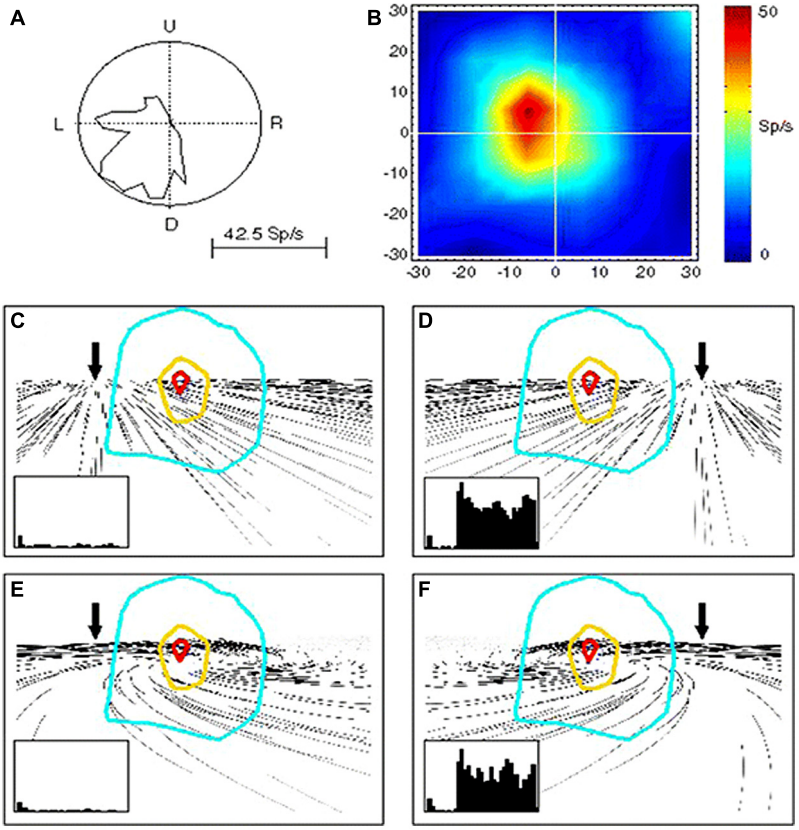


FIGURE 2 | Responses of a single MST neuron to unidirectional motion and optic flow. (A) Polar plot of the directional selectivity to left and downward motion. **(B)** Receptive field (RF) characterized by moving luminant bars to the left. **(C–F)** RF outlines on the visual flow stimuli reproducing leftward **(C,E)** and rightward **(D,F)** heading with **(E,F)** and without **(C,D)** eye movements. In the insets are shown the neuron responses in each condition. Note that the neurons is reliably responding to rightward heading (leftward visual flow) **(D,F)** and not to leftward heading (rightward visual flow) irrespective of the eye-movement-related distortion. Reproduced from Bremmer et al. (2010).

In humans, similar findings have been reported in a cortical network including the homolog of the motion sensitive areas MST i.e., the area BA 37 in the anterior bank of the inferior temporal sulcus (Bense et al., 2001; Huk et al., 2002; Stephan et al., 2005), the medial parietal cortex V6 and the VIP that might support heading perception (Morrone et al., 2000; Baumann and Mattingley, 2010; Cardin and Smith, 2010, 2011; Cardin et al., 2012; Smith et al., 2012; Indovina et al., 2013). However, using functional MRI, Cardin et al. (2012) suggest that only MST is implicated in the extraction of optic flow for computation of heading direction. While MST might provide a representation of heading perception, V6 would rather be concerned with obstacle avoidance during self-motion as inferred by Cardin et al. (2012). By using galvanic stimulation in humans, Smith et al. (2012) have described vestibular inputs in two cortical regions localized in the anterior part of MST and the visual area of cingulate cortex (CSv). Furthermore, by investigating the cortical activation elicited during vection, Brandt et al. (1998) showed that visual-vestibular interactions could take place in the extrastriate visual cortical areas, including the human homolog of MST in BA37. Thus, in order to disambiguate self-motion from object motion, reciprocal excitatory-inhibitory influences would occur within cortical loops including visual extrastriate cortex (MST) and vestibularly activated cortex i.e., temporo-parietal and retro-insular cortex (Brandt et al., 1998; Galati et al., 1999; Kleinschmidt et al., 2002). Brandt et al. (1998) have concluded that the intracortical visuo-vestibular interactions might insure self-motion sensation during body displacements and the opposite during motion of the visual field by respective inhibition of the visual or the vestibular retro-insular cortex.

So far, if self-motion encoding seems to emerge from the activity of the superior temporal cortex, very few studies report on a possible top-down regulation by this region on visuo-vestibular-related structures. As described above, Dursteler and Wurtz (1988) have shown that chemical lesions in MST produce deficits in OKN induced by large visual field displacement. Otherwise, possible top-down influences are suggested by the existence of projections from the parieto-temporal cortex to the subcortical vestibular complex in monkey (Ventre and Faugier-Grimaud, 1988). Interestingly, by analyzing the topography of the injection sites in the parieto-temporal cortex, MST might have been encroached upon by our injections including the postero-ventral part of the parietal cortex and the dorsal banks of the

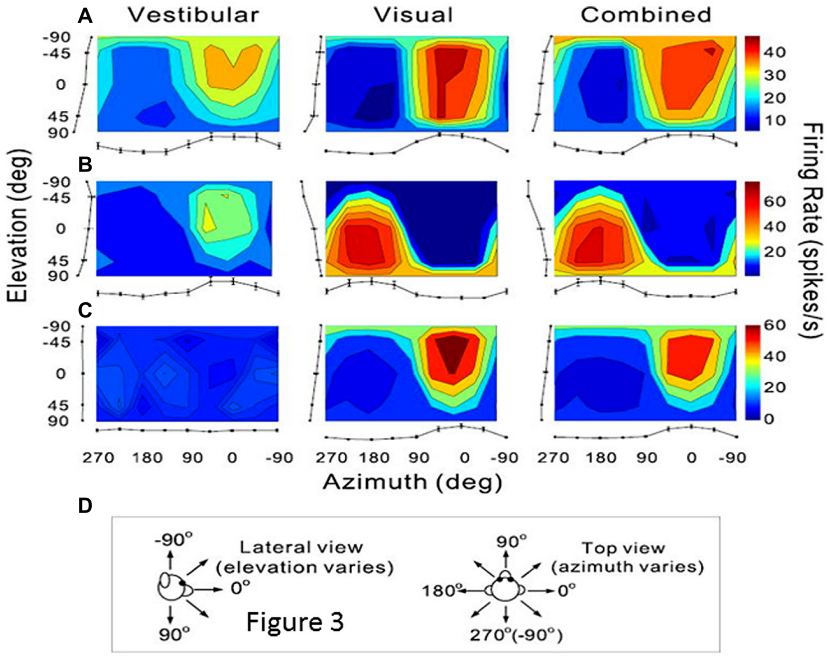


FIGURE 3 | Vestibular and visual tuning of three MST neurons responding to heading directions defined respectively by inertial motion alone (vestibular), optic flow alone (visual), and congruent combinations of the two cues (combined). (A–C) Tuning curves showing the firing rates (mean + SEM) represented as the margins of each color map and plotted as a function of the heading direction computed in azimuth and elevation angles. **(D)** Representations of the 3D heading directions in azimuth and elevation angles. **(A)** Neuron with congruent tuning for heading elicited by vestibular and visual cues. **(B)** Neuron with incongruent tuning for heading elicited by vestibular and by visual cues. **(C)** Neuron with selective tuning for visual heading only. Reproduced from Gu et al. (2006).

superior temporal sulcus (Faugier-Grimaud and Ventre, 1989). As illustrated in **Figure 4** these parieto-temporal cortical sites were found to be directly projecting onto the vestibular nuclei complex including the medial vestibular and PH nucleus involved in the velocity storage integrator and gaze holding processing (Cheron et al., 1986a,b; Cannon and Robinson, 1987; Ventre and Faugier-Grimaud, 1988; Faugier-Grimaud and Ventre, 1989; Yokota et al., 1992). Interestingly, the connections from some extrastriate visual areas including MST responsible for visual motion processing in the far periphery might mediate rapid-response related information for orienting and postural reactions (Palmer and Rosa, 2006).

As a whole, the extrastriate areas including the middle superior temporal area (MST) are clearly implicated in processing movement information during ego-motion. In order to compensate for body displacements, the MST region in complement to other visual-vestibular cortical sites will preferentially compute velocity signals issued from the retina or head sensors and consequently it might contribute to eye/head coordination during rapid body orientation. This temporal cortical pole related to self-motion perception and rapid eye/head coordination might form a dissociated path from the parietal cortical pole whose implication in inertial vestibular signal integration and space representation will be considered in the following section. There, we will try to identify and assemble the functional features of this parieto-temporal region suggestive of integration (e.g., velocity to position) of visual and vestibular signals in the context of space representation.

IS THE PARIETAL CORTEX IMPLICATED IN AN INERTIAL PROCESSING PATHWAY?

IDENTIFICATION OF A VESTIBULAR PARIETO-TEMPORAL NETWORK

The first evidence of a pure vestibular cortical field was provided by evoked potentials techniques in the cat (Walzl and Mountcastle, 1949). These authors showed that a neuronal activity could be evoked by vestibular nerve stimulation in an anterior area of the suprasylvian sulcus, anterior to the auditory area and to the motion analysis suprasylvian cortex previously described. These observations in animal were in line with a temporal lobe hypothesis of a vestibular cortex suggested in human patients after cortical damage (Carmichael et al., 1954) or after electrical stimulation (Penfield and Jasper, 1954) of the temporal lobe. By electrophysiological recordings in the cat and in the monkey (Kornhuber and Da Fonseca, 1964; Fredrickson et al., 1966, 1974) single units were identified in the somatic area 2v that respond to caloric or galvanic labyrinthine stimulation.

A clear description of vestibular cortical fields were provided in behaving animals in the early 1980s by Mergner (1979) in the cat anterior suprasylvian cortex and by Kawano and Sasaki (1984), Kawano et al. (1980, 1984) in the macaque parietal associative cortex. Thus these electrophysiological recording studies provided evidence that vestibular inputs were integrated in cortex during sinusoidal rotation (Becker et al., 1979; Kawano et al., 1980). In Java monkey, Grusser et al. (1990a,b) identified neurons activated preferentially during angular acceleration in a separate

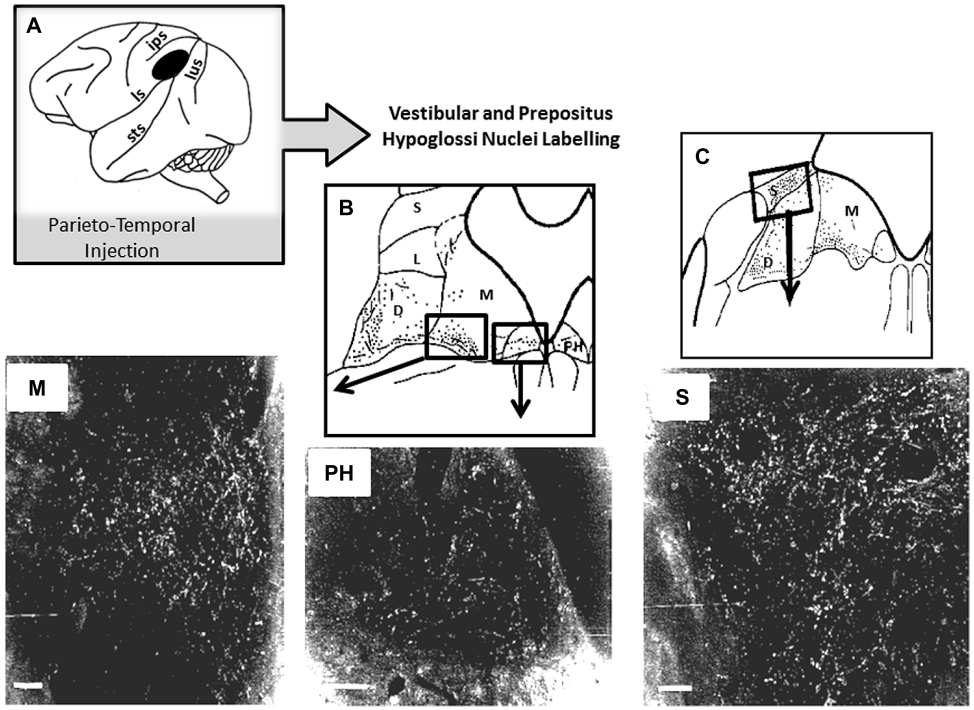


FIGURE 4 | Horseradish peroxidase (HRP) anterograde labeling in vestibular complex and prepositus hypoglossi in macaque monkey. **(A)** Schematic representation of the location of the HRP injection site in the parieto-temporal cortex. **(B,C)** Reconstruction of the labeled zones in the vestibular complex and in the prepositus hypoglossi. In the bottom part, darkfield photomicrographs display bright labeled neurons and fibers in the medial (M) and superior (S) vestibular nuclei and in the prepositus hypoglosi nucleus (PH). Insets are showing the locations in the brainstem where the photomicrographs have been taken. Adapted from Ventre and Faugier-Grimaud (1988).

region localized in the parieto-insular cortex. The authors called this region the parieto-insular vestibular cortex (PIVC) which they demonstrated further to be directly connected to the vestibular nuclei complex in the brainstem (Akbarian et al., 1994). At the same time, behavioral studies on the effects of focalized lesions in the parietal cortex confirmed Kawano's observations (Kawano et al., 1980). Indeed, by using a unilateral cortical lesion approach (Ventre and Faugier-Grimaud, 1986), we demonstrated that unilateral damage of the postero-lateral part of area 7 in monkey induced vestibulo-ocular disturbances similar to those observed after a unilateral damage of the cortical homolog in the cat, the middle suprasylvian cortex (Ventre, 1985b). Such top-down effects on vestibulo-oculomotor function were confirmed as we found direct projections from this parietal cortex (previously lesioned: Ventre and Faugier-Grimaud, 1986) onto the vestibular nuclei complex as well as on the prepositus hypoglossi nucleus (NPH) in monkey (Ventre and Faugier-Grimaud, 1988, Faugier-Grimaud and Ventre, 1989).

The existence of a large network of cortical areas projecting onto the vestibular nuclei was also demonstrated by further anatomical works in monkey (Faugier-Grimaud and Ventre, 1989; Akbarian et al., 1993, 1994; Guldin et al., 1993). **Figure 5** synthesizes the different findings related to cortical projections onto the vestibular nuclei complex and prepositus hypoglossi distinguishing ascending oculomotor projections from descending skeletto-motor projections. Therefore, in the posterior associative cortex of monkey, evidence was provided for two distinct sites: (1) a caudal site corresponding to the posterior part of area 7 and (2) a second more rostral site, in the retro insular cortex corresponding to the so-called PIVC. In humans, a number of neuroimaging studies (PET and fMRI) investigated the cortical activation induced by caloric or galvanic stimulation of healthy subjects (Bottini et al., 1994, 2001; Bucher et al., 1997; Lobel et al., 1998; Bense et al., 2001; Fasold et al., 2002; Dieterich et al., 2003; Emri et al., 2003; Stephan et al., 2005; Eickhoff et al., 2006; Lopez et al., 2012). A neural network similar to the one described in monkey was found to be distributed between the parietal, temporal cortex and prefrontal cortices. While the postero-lateral part of the monkey parietal cortex is likely to correspond to the parieto-temporal cortex including area 39–40 on the parietal convexity (Ventre and Faugier-Grimaud, 1986, Faugier-Grimaud and Ventre, 1989; Kahane et al., 2003; Ventre-Dominey et al., 2003), the human analog of PIVC described in the posterior end of the insula in monkey remains quite uncertain. A number of neuro-imaging studies have suggested that the PIVC could correspond to the retro-insular cortex in humans (Dieterich and Brandt, 2001; Fasold et al., 2002; Stephan et al., 2005). However, based on correlations between functional imaging and cytoarchitectonic data, such an analogy has been recently revisited (Eickhoff et al., 2006; Zu Eulenburg et al., 2012) as the authors have localized in the posterior parietal operculum- the OP2 area- a putative human PIVC region (Grusser et al., 1990a,b). Accordingly, by using electrical stimulation in epilepsy patients,

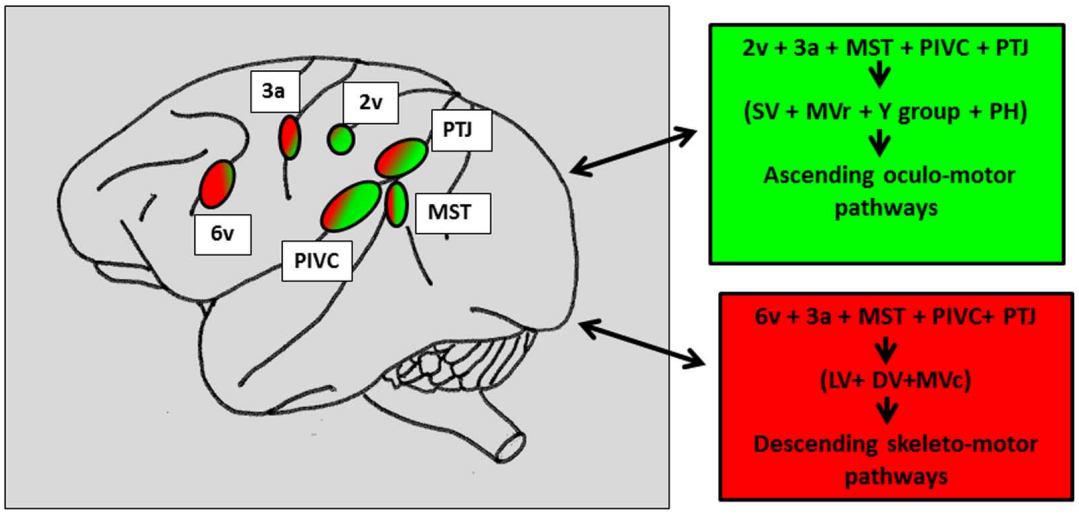


FIGURE 5 | Schematic representation of the vestibular cortical sites directly connected to the vestibular nuclei and the prepositus hypoglossi in macaque brain. In the right panels: Projections topographically organized with the caudal vestibular cortical fields including MST, RI, and TPJ projecting more in the vestibular and prepositus hypoglossi nuclei, involved in the oculomotor ascending pathways (green patches) as compared to the more rostral cortical fields connected to the vestibular nuclei mainly involved in the skeletto-motor descending pathways (red patches). The numbers refer to the architectonically defined Brodman's cortical areas. PTJ, Parieto-temporal junction; MST, middle superior temporal area; PIVC, parieto-insular vestibular cortex; Superior (SV), medio-rostral (MVr), medio-caudal (MVc), lateral (LV) and descending (DV) vestibular nuclei. Prepositus hypoglossi (PH) nucleus. Reconstructed from previous findings from Ventre and Faugier-Grimaud (1988), Akbarian et al. (1994).

Kahane et al. (2003) could induce vestibular sensations by stimulating the temporo-parietal cortex close to the parietal operculum and less so the retroinsular cortex. Consequently, in the following we will refer to the parietal operculum i.e., the OP2 area, as the human cortical homolog of PIVC. At this point of our knowledge related to the organization of the vestibular cortex in primate, a question can be raised: whether these two parietal cortex (on the cortical surface) vs. parietal operculum- OP2- (in the sulcal depth) sites are functionally distinct or belong to a common cortical parietal network involved in vestibular function? So far, even though numerous studies including human investigations confirm the parietal involvement in vestibular function, the exact functional contribution of its different fields (TPJ vs OP2) remains unclear.

VESTIBULAR INTEGRATION IN THE PARIETO-TEMPORAL NETWORK AND SPATIAL PROCESSES

Representation of the extrapersonal space

The temporo-parietal cortical junction constitutes a major hub of multi-sensory convergence and transformations underlying spatial representation. Such a role of the parietal cortex in spatially oriented behavior has been revealed by the neglect syndrome that can develop in patients after right parietal damage (for review, Karnath and Dieterich, 2006; Karnath and Rorden, 2012). A visuo-spatial neglect is a neurological disorder characterized by a difficulty for patients with a right brain injury to respond or orient themselves to persons or objects located in the contralesional space. Neglect patients usually exhibit spontaneous and sustained deviation of their eyes and head toward the side of the brain damage. Even though neglect syndrome was often linked to right parietal damage, structural brain imaging demonstrates the involvement of a perisylvian cortical network including the parieto-temporal junction, the inferior parietal lobe, the superior/middle temporal cortex and the ventrolateral prefrontal cortex. Interestingly this cortical perisylvian network partially overlaps with the temporo-peri-Sylvian vestibular network defined by Kahane et al. (2003) on the basis of vestibular symptoms evoked in a large group of epileptic patients. This peri-Sylvian vestibular network would preferentially process vestibular canal signals that transduce angular head accelerations (Kahane et al., 2003). The similarity in the topographical aspects of the neglect vs vestibular peri-sylvian networks is also paralleled with a similarity in behavioral deficits, i.e., ipsilesional eye and head deviation observed in neglect patients as well as in patients with peripheral vestibular loss. Furthermore, it has been shown that a durable compensation of the neurological spatial disorders can occur after unilateral labyrinthine stimulation in neglect patients (Rubens, 1985; Vallar et al., 1995). In keeping with this idea of a linkage between parieto-temporal cortex, visuo-spatial, and vestibular functions, we have shown vestibulo-ocular deficits in patients with unilateral parieto-temporal lesions (Ventre-Dominey et al., 2003). As illustrated in **Figure 6**, the vestibular deficits were preeminent for the inertial components of the vestibulo-ocular reflex (the time constant and bias) and were significantly linked to visuo-spatial disorders (Ventre-Dominey et al., 1999, 2003). Accordingly, by using a novel paradigm combining bistable perceptual stimuli or complex attentional tasks with concurrent vestibular stimulation in healthy human subjects, Arshad et al. (2013) report similar findings suggestive of a top-down cortical regulation of the VOR time constant. In a patient with a residual neglect consecutive to an occipito-parieto-temporal damage, the ability to update the contralesional visual

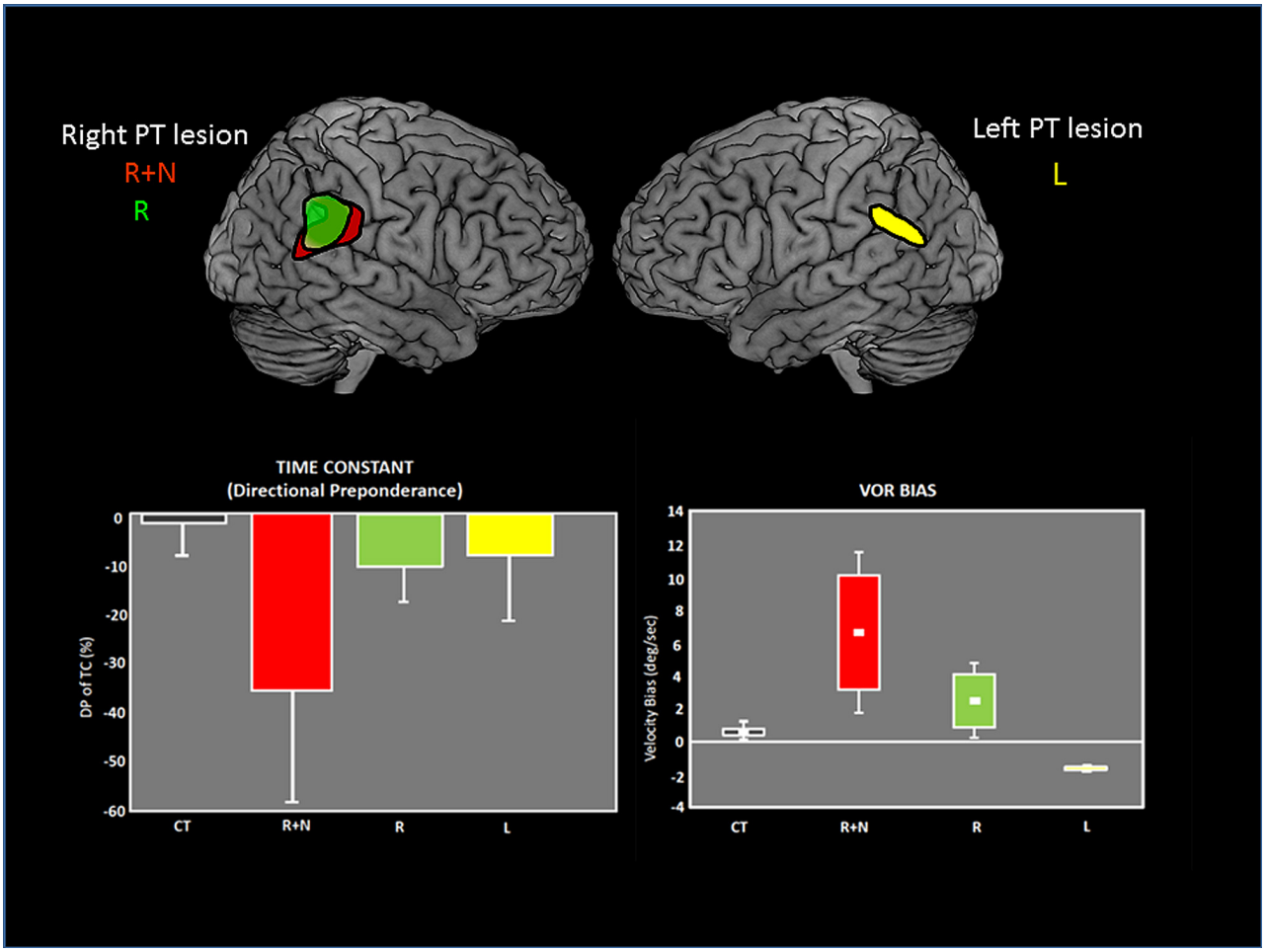


FIGURE 6 | Vestibulo-ocular (VOR) deficits observed in patients after unilateral lesions in the parieto-temporal junction. On the top, the common lesioned sites have been reconstructed and are represented for each group of patients on the lateral views of brain templates: R+N: right lesion with neglect. R: right lesion without neglect. L: Left lesion. On the bottom, graphs showing the asymmetrical deficits in VOR time constant (measured by the directional preponderance) and the VOR bias in each patient group. The deficits are majored with right lesions with neglect. Adapted from Ventre-Dominey et al. (2003).

space after angular rotation was perturbed (Ventre-Dominey and Vallee, 2007). In normal subjects, Seemungal et al. (2008), Seemungal (2014) found that repetitive transcranial magnetic stimulation (rTMS) of the right parietal cortex (comparable to a virtual lesion) disrupted the perceptual encoding of vestibularly driven displacement in contralateral space. On the basis of these observations we infer that the parieto-temporal cortex exerts a down regulation of the vestibulo-ocular function in particular the inertial (low frequency) component implying the velocity storage integrator.

Evidence for the top-down influence of the parieto-temporal cortex in primate is strengthened by the existence of direct anatomical pathways connecting this part of the posterior cortex to the vestibular nuclei complex (**Figure 4**). Indeed, we have demonstrated in monkey that the parietal cortex located posteriorly to the PIVC projects directly onto the vestibular nuclei including the medial vestibular and PH nuclei involved in the velocity storage integrator and gaze holding processing (Cheron et al., 1986a,b; Cannon and Robinson, 1987; Ventre and Faugier-Grimaud, 1988; Faugier-Grimaud and Ventre, 1989; Yokota et al., 1992). Based on our findings and those of the recent literature, we suggest that the parietal cortex constitutes a unique cortical region involved in high-ordered multimodal transformation of inertial vestibular signals including the updating of the visual space during body displacements.

Representation of self-referential space

The idea of a vestibular influence in space representation involving the parieto-temporal cortex has been extended to self-referential processing by a series of experiments using illusory percepts (Blanke and Arzy, 2005; Tsakiris and Haggard, 2005; Ionta et al., 2011a,b, Lopez and Blanke, 2011). For example, the most commonly described experiment the so-called rubber-hand illusion demonstrates how a sensory conflict between visual and tactile signals can produce changes in bodily self-referential (Tsakiris and Haggard, 2005). In the rubber-hand illusion, the participant is

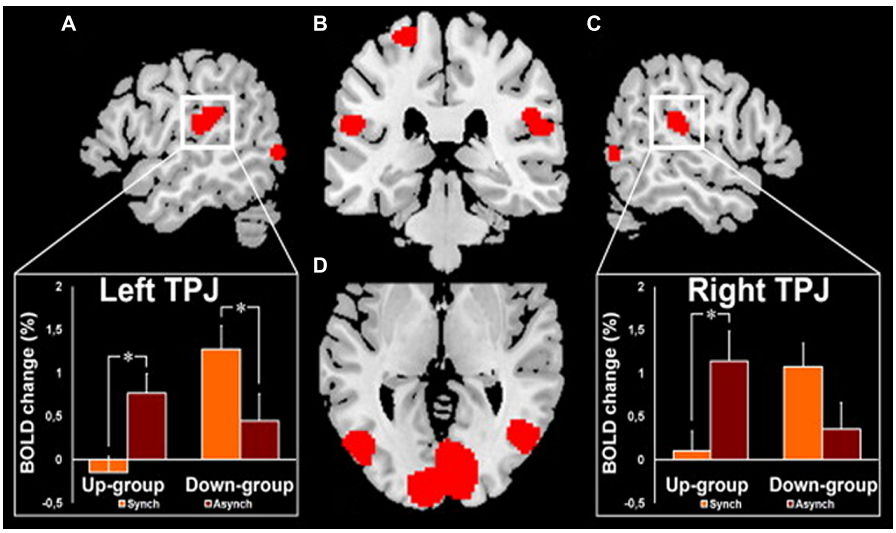


FIGURE 7 | fMRI activation in the right and left temporo-parietal junctions (TPJ) in healthy subjects during experimentally induced out of body experience (OBE). In the Up-group, the subjects experience themselves to look upward at a visually presented body and to be spatially higher with the synchronous as compared to the asynchronous stroking of their back. In the Down-group, the opposite pattern of sensations is observed as the subjects experience themselves to look downward and to be spatially higher with the asynchronous as compared to the synchronous stroking of their back. The magnitude of the blood- oxygenation-level-dependent (BOLD) responses in the TPJ is lower in the condition of higher self-location in the synchronous and in the asynchronous stroking, respectively, for Up-group and for Down-group. **(A)** Left TPJ activation with inset showing the corresponding BOLD changes in each group and condition. **(B)** Activation in the left and right TPJ and in the left superior postcentral gyrus. **(C)** Right TPJ activation with inset showing the corresponding BOLD changes in each group and condition. **(D)** Bilateral activation of the posterior middle and inferior temporal gyri. *Significant differences and bars: standard errors. Reproduced from Ionta et al. (2011b).

looking at a stroked rubber hand while his/her own hidden hand is synchronously stroked. After a delay, the participant reports the sensation of his/her own hand to be positioned close to the fake hand, or even of an illusory ownership of it.

Interestingly, such an illusory perception of a false hand ownership is emphasized by galvanic vestibular stimulation using the same paradigm of the rubber-hand illusion (Lopez et al., 2010). Lopez et al. (2010) concluded that such a vestibular interference is mediated by the parieto-temporal and posterior insular cortex. In the same vein, clinical observations of out-of-body experiences (OBEs) suggest that localized cortical lesions can induce pathological changes of first-person perspective and self-location in space (Blanke et al., 2002, 2004; Blanke and Mohr, 2005; De Ridder et al., 2007). Similarly to the rubber-hand illusion, the OBE has been reproduced in healthy subjects by manipulating tactile and visual information on the back of their body (Ehrsson, 2007; Lenggenhager et al., 2007). In this experiment, by synchronously scrubbing the participant's back and the back of a visually displayed virtual body, changes in self-consciousness occur as the participant experiences a drift of the first person perspective and the self-location toward the virtual body. In a recent neuroimaging study, this same group (Ionta et al., 2011b) demonstrates that the illusory shift in bodily self-referential was reflected in changes in cerebral activation of the parieto-temporal cortex (TPJ) contiguous to the cortical area within the TPJ that is lesioned in OBE patients. As shown in **Figure 7**, these authors reported two kinds of OBE sensations: – in the Up-group, the subjects experiences themselves to be looking upward at the visually displayed body and estimated their self-location to be higher during a synchronous as compared to an asynchronous stroking of their back and – in the Down-group, the subject's experiences themselves to be looking downward at the visually displayed body and estimated their self-location to be higher during asynchronous as compared to synchronous stroking as some subjects. The TPJ blood-oxygenation-level-dependent (BOLD) response decreased in the Up-group only during the synchronous condition and the opposite for the Down-group with a decreased BOLD TPJ response in the asynchronous condition. Ionta et al. (2011b) suggest that the TPJ activity reflects drift-related changes in self-location within each group that depend differently on the experienced direction of the first-person perspective. The OBE percept has been linked to interactions between gravitational visual and vestibular cues which might take place in TPJ (Ionta et al., 2011b). Thus OBE might rely on the remapping of self-location in extra-personal space based on a double disintegration of bodily visual and vestibular signals taking place in the TPJ and the nearby posterior parietal operculum. These recent observations related to bodily self-consciousness stress the importance of the vestibular function in high-order multimodal processing taking place in the posterior cortex including the temporo-parietal junction possibly including the posterior parietal operculum.

CONCLUSION AND THEORETICAL PERSPECTIVES

In conclusion, this review on the different components of the lateral parietal and temporal cortex leads to the idea of two separate cortical vestibular fields as it is schematically represented in **Figure 8**:

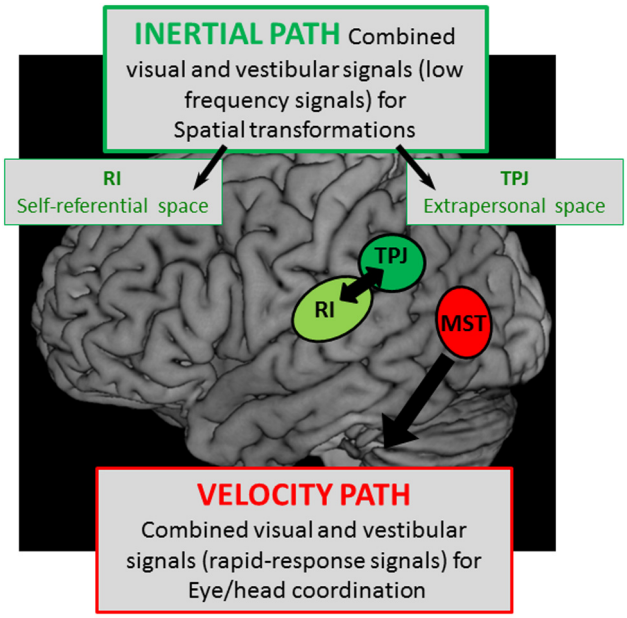


FIGURE 8 | Schematic representation of two hypothetical cortical pathways with – a velocity path including the middle superior temporal cortex (MST) where visual and vestibular signals are mediated to serve for rapid-responses during eye/head coordination, and – an integration pathway of visual and vestibular signals with low kinematic (low frequencies) in the temporo-parietal junction (TPJ) and the retro-insular cortex (RI) possibly involved in the construction respectively of the extrapersonal and self-referential spaces.

The first involves the extrastriate temporal area including MST which receives well-defined visual and vestibular velocity signals likely involved in heading perception. On the basis of the oculomotor kinetic-related properties and the lesion effects of this cortical region, it is likely that MST mediates both visual and vestibular information in order to compensate for head motion thereby contributing to eye/head coordination. Such a rapid top-down regulation of visuo-vestibular interactions might be subtended by direct descending pathways from MST to vestibular nuclei and prepositus hypoglossi involved in gaze control.

The second involves the parietal cortex including parieto-temporal junction and posterior parietal operculum, both implicated in high-order multimodal integration and cognitive functions, including peri-personal space and self-referential processing. In this context, the vestibular information would be processed in the parietal cortex in connection with the subcortical vestibular nuclei complex for a velocity storage integration that might contribute to the construction of spatial reference frames. Such an integration pathway might be responsible: (1) for extrapersonal space transformations preferentially in the parieto-temporal junction subtending visuo-spatial orientation and (2) for self-referential processing involving the bodily information about self-location in space that might be mediated preferentially by the parieto-opercular pole of this local vestibular parietal network.

These posterior vestibular fields are likely part of a more extended cortical network, such as the peri-sylvian network described above and implicated in high-order cortical processes linked to spatial referential processing. Moreover, if such a hypothetical cortico-vestibular architecture involved in cognitive functions has been built on the basis of the literature review, this hypothesis forms the basis for a program of future research.

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Vestibular activity and cognitive development in children: perspectives

Sylvette R. Wiener-Vacher[1], Derek A. Hamilton[2] and Sidney I. Wiener[3,4]*

[1] *Vestibular and Oculomotor Evaluation Unit, Department of Otorhinolaryngology, Robert Debré Pediatric Hospital, Paris, France*
[2] *Department of Psychology, University of New Mexico, Albuquerque, NM, USA*
[3] *Laboratoire de Physiologie de la Perception et de l'Action, UMR-7152, Centre National de la Recherche Scientifique - Collège de France, Paris, France*
[4] *Memolife Laboratory of Excellence, Paris Science and Letters University, Paris, France*

Edited by:
Paul Smith, University of Otago Medical School, New Zealand

Reviewed by:
Cynthia Darlington, University of Otago, New Zealand
Paul Smith, University of Otago Medical School, New Zealand

***Correspondence:**
Sidney I. Wiener, Laboratoire de Physiologie de la Perception et de l'Action, UMR-7152, Centre National de la Recherche Scientifique - Collège de France, 11 Place Marcelin Berthelot, 75231 Paris Cedex 05, France
e-mail: sidney.wiener@college-de-france.fr

Vestibular signals play an essential role in oculomotor and static and dynamic posturomotor functions. Increasing attention is now focusing on their impact on spatial and non-spatial cognitive functions. Movements of the head in space evoke vestibular signals that make important contributions during the development of brain representations of body parts relative to one another as well as representations of body orientation and position within the environment. A central nervous system pathway relays signals from the vestibular nuclei to the hippocampal system where this input is indispensable for neuronal responses selective for the position and orientation of the head in space. One aspect of the hippocampal systems' processing to create episodic and contextual memories is its role in spatial orientation and navigation behaviors that require processing of relations between background cues. These are also impaired in adult patients with vestibular deficits. However little is known about the impact of vestibular loss on cognitive development in children. This is investigated here with a particular emphasis upon the hypothetical mechanisms and potential impact of vestibular loss at critical ages on the development of respective spatial and non-spatial cognitive processes and their brain substrates.

Keywords: ontogeny, development, vestibular, otolith, cognitive, navigation, human

INTRODUCTION

How does loss of vestibular function at various ages of childhood impact on the development of complex spatial behaviors and cognition? To respond to this, it is necessary to chart the ontogeny of these behaviors and of the brain structures implicated in their expression. Bilateral loss of vestibular function at or close to birth results in motor developmental delays (Rine et al., 2000; Whitney et al., 2009; Wiener-Vacher et al., 2012b). Although vestibular loss can be compensated with a return to normal postural and oculomotor functions, observations of such children throughout childhood reveal that many of those with complete vestibular loss exhibit learning disabilities and poorly adapted strategies for overcoming their sensory deficit (Franco and Panhoca, 2008). For example, the gaze and fixation problems associated with vestibular dysfunction can lead to reading problems requiring specific therapy (Braswell and Rine, 2006). Development of diverse cognitive functions could be impaired in vestibular-deficient children through several possible mechanisms. For example, vestibular deficits can impair detecting and distinguishing one's own movements from other movements in the environment through both the visual and proprioceptive systems.

It has also been hypothesized, similar to the "critical periods" observed for visual system development, that other cognitive functions also have limited developmental windows when their underlying brain structures establish long-lasting connectivity with repercussions for life. During movements, sensorimotor loops transmit conflicting or inaccurate information in vestibular-impaired patients and this could lead to faulty wiring and deficits in cognitive function. This chain of events can be conceptualized in a framework where high level brain representations are built up from sensorimotor loop activity by intermediate representations of emulated or imagined actions in the real world and their anticipated outcomes.

Vestibular patients have difficulties in constructing and using several types of brain representations of space. Adults with bilateral vestibular lesions have hippocampal atrophy and suffer spatial and non-spatial cognitive impairments (Schautzer et al., 2003; Brandt et al., 2005). Do critical periods exist during development where vestibular signals are required to establish normal hippocampal circuitry permitting spatial navigation and other functions? To address this issue, theoretical background will first be provided on the forms of spatial navigation, noting how they are supported by the diverse types of vestibular information. Next we will discuss the hippocampal system, its spatial representations, its relations with the vestibular system and its development, followed by a review of developmental studies of performance in specially designed spatial orientation tasks. The final section will tie this all together, leading to specific predictions of the impact of vestibular damage on spatial cognition at respective ages corresponding to milestones in brain and cognitive development. This will be considered in terms of early identification of the potential cognitive deficits deriving from vestibular disorders, thus permitting better adapted therapy and training programs.

Vestibular inputs provide several types of information which are respectively engaged for diverse corresponding sensorimotor and cognitive processes (Potegal, 1982; Wiener and Berthoz, 1993; Borel et al., 2008). The three pairs of semicircular canals and the otolith organs provide complementary information about several types of rotational and translational head movements involving accelerations and, importantly, signal the direction of gravitational force. The latter is fundamental to terrestrial life from birth since postural adjustments and active movements invariably must take gravity into account. The brain builds representations of verticality based upon vestibular, somatosensory proprioceptive, and visual information, constructing a "geocentric" reference frame (Borel et al., 2008). Vestibular patients are thus handicapped in acquiring information during active displacements in the environment since sensory frames of reference (e.g., visual or proprioceptive; Lacour et al., 1997; Isableu et al., 2010) must be established without vestibular information. Furthermore, gravitational and other vestibular information can be instrumental in timely acquisition of fundamental spatial relationships of up vs. down, left vs. right, front vs. back, etc. (Wiener-Vacher et al., 2012a). Infants first learn these spatial relations with reference to their own body. Understanding spatial relations between the body parts is difficult for vestibularly impaired infants, perhaps in part because proprioceptive information about gravity is not reinforced by otolithic gravity sensation. This would then have a negative impact on understanding other spatial relationships such as over/under, inside/outside, within/without, interposition, etc. These patients would then have difficulty applying these concepts for establishing coordinate systems for representing the relative positions and orientations between environmental features and their own relative position and orientation to all of this. Furthermore, if concepts like "close, distant, superior, inferior, etc." are poorly understood, the child could also have difficulty extending them to arithmetic and geometry as well as to other non-spatial domains where sets and groups are compared (e.g., syntax, biology, history).

The vestibular system also makes a vital contribution in helping to distinguish visually perceived self-movements from movements of objects in the environment. Vestibular inputs help to reconcile diverse and conflicting signals including vision, proprioception (and other somatic sensation) and internally generated motor commands. For example, *optic flow* signals are generated when the head moves slowly at a constant velocity, but they also occur when the head is immobile by viewing clouds drifting across the sky, movement of the environment as seen from a stroller or a car window, by points of light projected by a rotating disco mirror ball, by movements of crowds, while seated on an immobile train when the train on the next track pulls away, etc. Difficulties in reconciling self-movements from non-self-movements as well as in selecting appropriate vertical and horizontal references can thus lead to problems in postural and motor coordination, fine motor control, and visual processing. Vestibular patients depend more on vision and proprioception for determining the earth vertical orientation and if an object taken to be a stable reference point moves, this can lead to postural instability and disorientation.

Signals related to rotational and linear accelerations including gravity can help stabilize and inform several types of movements. Each of these is associated with cognitive processes that can lead to distinctive types of problems in cases of vestibular impairments. These movement types include:

(a) gaze stabilization during passive and active head and body movements,
(b) maintaining equilibrium: stable head on neck and body posture during immobility and movements, both passive and active,
(c) relative movements among body parts (head on neck, pointing, touching parts of head and body),
(d) locomotion,
(e) interaction with the environment (pushing, reaching, catching, ducking/avoidance, etc.).

Impairment or late development of these functions would also deprive the patient of the sensorimotor feedback information generated by these movements. For example, infants without otolith function learn to walk later than controls (Wiener-Vacher et al., 2012b) and fall more frequently. This developmental deficit means that they do not receive timely and coordinated visual and proprioceptive feedback associated with stable walking – information that would be vital for building spatial representations. An infant with a vestibular deficit, who typically walks very cautiously and attentively, seeking mechanical support and maintaining a rigid neck, is not able to learn as much about spatial relationships in the environment, and thus will have less opportunity to build internal representations of space. For example, distances are often calibrated in numbers of paces, but this is not feasible for these patients. One theoretical framework of how cognitive representations emerge in the brain contends that sensorimotor loop activity is internally simulated and re-represented in the absence of the relevant sensory inputs and movement. This would lead to anticipatory processes and the construction of yet higher level representations. Since vestibular dysfunction would impair the many sensorimotor processes described in the previous paragraphs, serious consequences can be expected in building representations and cognitive processing in the corresponding functional domains.

Before reviewing the literature relevant to the question of the developmental consequences of vestibular impairments, it is necessary to re-emphasize that the semicircular canals and otolith organs respectively provide fundamentally different information. In particular, only the otoliths are specialized for detecting the direction of gravity force crucial for establishing vertical orientation and thus defining spatial reference frames in concert with the axes of the rotational selectivity of the semicircular canals. In the vast majority of the literature, the *patients groups described as "vestibular impaired" were tested for semicircular canal function only. Thus it is possible that residual otolith organ function remained in some reportedly vestibular-deficient patients – and that some reportedly normal controls had functional canals but no otolithic responses.* Even for experimental subjects who have had surgical labyrinthectomies or neurectomies, it is advisable to perform comprehensive vestibular testing to verify that there is no residual function. A second issue is that patients show a great deal of variability in their degree of compensation due to unequal access to adapted training or therapeutic life experiences. It is possible that individuals may differ in central compensation processes

– evidence has been found for increases in volume in bilateral connections between the vestibular nuclei, in proprioceptive processing area of right gracile nucleus and the visual motion processing area MT/V5 (zu Eulenburg et al., 2010). Furthermore some may simply learn more effectively to substitute other cues such as visual field flow, various types of proprioceptive cues, visceral enteroception, visual landmark cues, and various vertical/horizontal cues. These caveats should be recalled in interpreting results from the literature and in planning new experiments.

TYPES OF NAVIGATION PROCESSING

Orienting cues can be considered in two categories by virtue of whether they transmit information about self-motion or about environmental characteristics. Self-motion cues come from the vestibular system, enteroceptors (located in the abdomen), motor efferent collaterals related to locomotion and orienting movements, proprioception countering gravitational forces and also transmitting traction or slippage of paws or feet against the substrate during locomotion. Although the vestibular system is only sensitive to rotational or linear acceleration of the head, the brain mathematically integrates these inputs over time first to provide velocity signals, and then again to detect the angle rotated and the linear distance covered. These integrations are subject to drift errors and are generally not reliable for displacements lasting longer than about 10 s, requiring regular corrective updates, for example, by consulting with visual cues. Studies of animals passively displaced then required to return to their nest show that rotations are taken in account more than translations (Etienne et al., 1988). Another important self-motion signal comes from optic field flow. This is the coherent movement of the image of the entire visual field relative to the eyes during head movements and it indicates the velocity of the head in space. While optic flow derives from visual detection of environmental cues, it cannot be accurately described as "allocentric." In vestibular rehabilitation therapy, patients learn to substitute the various visual and proprioceptive cues described above. Finally, information about the environmental layout comes chiefly from visual perceptions of objects, audition, and in certain species, magnetic sense, echolocation, and other exotic senses.

Diverse types of navigation strategies engage distinct cognitive processes (Trullier et al., 1997). Firstly, in *dead reckoning*, or *path integration*, the initial starting point is noted. Then while traveling, the velocity is integrated over time to compute the distances covered. Angular heading during these displacements is taken into account by vectorial addition yielding the total displacement as a result (and reversing this gives the return vector). Principal sources of information are the self-motion cues described above, including the vestibular sense. Correct estimation of the duration of time is clearly crucial for this integration (Israël et al., 2004).

The *body alignment and target approaching* navigation strategy, also referred to as *beacon homing*, *piloting*, or *approach/avoidance*, involves moving toward (or away from) a cue or object in the environment. In the *guidance* strategy (as defined by O'Keefe and Nadel, 1978), the animal maintains a certain egocentric relationship with respect to a particular landmark or object. A vestibular patient with oscillopsia (continual oscillation of the visual field) might be expected to have difficulty with this.

The next categories of navigation strategy are more advanced since they can be used to reach a known but not currently visible goal and involve identification of and orienting relative to *places*. A place is defined within a large-scale environment as a set of contiguous locations that are equivalent with regard to action selection (Trullier et al., 1997). A place can also be defined as the set of locations from which a set of landmarks or a landmark configuration is perceived as identical or very similar. Thus implicit to this is a capacity to make generalizations. The term *place navigation* refers here to navigation toward a specific location based on its spatial relationship to a constellation of exteroceptive cues, particularly distant background visual cues. Other strategies such as piloting or vector-based navigation (Pearce et al., 1998) can be distinguished from place navigation in that no single cue is sufficient for place navigation.

Returning to the types of navigation processes, in *place recognition-triggered responses*, the origin and intermediate places along the route each have an associated angle of departure and distance to go to the next place. *Topological navigation* involves three steps: (a) recognizing the place where one is currently situated; (b) orienting within this place; and (c) selecting in which direction to move so as to reach its current goal. It is not necessary to plan a sequence of subsequent movements, but only to select the very next action. *Metric navigation* implies a veridical internal map that is consulted for making the most efficient changes in position.

VESTIBULAR DYSFUNCTION AND DEFICITS IN COGNITIVE FUNCTIONS INCLUDING NAVIGATION

Vision is a primary sensory modality in humans for detecting size, shape, distance, and layout information. Static and dynamic visual acuities are impaired by vestibular deficits. The ability to maintain a stable visual image while the head is moving, such as during walking, is dependent upon visual and vestibular inputs triggering eye movements opposing and compensating for head movements. When vestibular function is normal, visual acuity is similar whether the head is moving or stationary. The difference in static and dynamic visual acuity (DVA) can be quantified using the DVA test (Schubert et al., 2006). Adults and children with vestibular deficits have impaired DVA (Rine and Braswell, 2003; Herdman et al., 2007). Vestibular deficits are characterized by an absence of the vestibulo-ocular response which maintains gaze fixed on a target when the head is passively moved suddenly in the direction of sensitivity of a vestibular receptor end organ. This is the basis of the commonly used clinical head impulse test (HIT) for detecting vestibular deficits (Halmagyi et al., 1994). Subjects with complete vestibular loss complain of oscillopsia during movements – this makes them dizzy and disoriented when they walk, run, drive, and read. Indeed, Braswell and Rine (2006) reported that children with vestibular deficits have poor DVA results and this is associated with significant reduction in reading acuity. Smooth pursuit oculomotor activity can compensate for head rotations up to a velocity of 100°/s. However, above this speed only the vestibular system can detect and compensate for movements, and this range of sensitivity is needed for many activities of daily life. Indeed,

walking induces much low amplitude but high acceleration and velocity vibration and shaking of the head (as apparent in a movie taken from a camera carried on one's shoulder) and the vestibular system permits this to be transformed to a smooth continuum.

In addition to problems related to vision, vestibular deficits can lead directly to difficulties in estimating angular and distance displacement, presumably through path integration. Beritoff (1965) observed navigation deficits in children and in experimental animals with no detectable semicircular canal function. In cases where the animals were familiar with a trajectory to a reward site, in the absence of vision, they no longer were able to go directly to the learned reward site. When vision was restored, they resumed taking the direct path. Children aged 10–12 years old were blindfolded, led or carried along a trajectory then along the return path. They were able to retrace the steps, while blindfolded children with non-functioning labyrinths could not, even after several trials. This is one of the rare studies examining cognitive deficits in vestibular-impaired children; the following text examines the literature concerning adults. These studies show that vestibular patients have difficulties in detecting and estimating body displacements in the dark. During goal-directed locomotion, these patients make errors in trajectory (e.g., Borel et al., 2004; Cohen and Sangi-Haghpeykar, 2011). Another test where they have difficulty is reversing the trajectory along a triangular path or finding a shortcut (Péruch et al., 1999, 2005; Glasauer et al., 2002; Guidetti et al., 2007; for review, see Israël and Warren, 2005).

In experiments evaluating dead reckoning, rats were required to make return trips to a hidden start location under dark conditions (Wallace and Whishaw, 2003). The peak velocity was observed at the point midway of this return trajectory and the direction of this trajectory was highly accurate, suggesting the computation of both the distance and direction to return to a target point of origin, consistent with dead reckoning. In similar experiments this team also demonstrated that dead reckoning is impaired after chemical labyrinthectomy (Wallace et al., 2002).

A great deal of contemporary understanding of place navigation and its neurobiological bases has come from research using the Morris water maze task (Morris, 1981, 1984; Sutherland and Dyck, 1984). In this task, rodents (typically rats) learn to navigate to an escape platform submerged in a circular pool of cool, opaque water. Because the circular pool provides only information about radial distance from the border, animals learn to navigate to the escape platform by way of reference to a constellation of visual cues outside the pool.

Over the past 15 years, several laboratories have utilized computerized, virtual, navigation tasks based on the Morris water task to measure place navigation in humans (Astur et al., 1998; Jacobs et al., 1998; Hamilton and Sutherland, 1999; Doeller and Burgess, 2008; Doeller et al., 2008; Mueller et al., 2008; Hamilton et al., 2009). The participants view an environment from a first-person perspective and "swim" in the virtual space using a keyboard or joystick. As in the Morris water maze, the environment contains distal visual cues and the subject must navigate to a hidden goal. These tasks have been shown to both engage (Cornwell et al., 2008; Doeller and Burgess, 2008) and require an intact hippocampus (Astur et al., 2002; Driscoll et al., 2003; Hanlon et al., 2006). The computerized virtual Morris water task (VMWT) has been used to characterize spatial memory deficits in patients with developmental disturbances (e.g., fetal alcohol syndrome, Hamilton et al., 2003) and psychiatric disorders (e.g., schizophrenia, Hanlon et al., 2006). Hartley et al. (2003) found fMRI activation in the hippocampus of human subjects during a virtual wayfinding task. Human subjects performing a virtual task requiring them to point to the origin of a trajectory along two sides of a triangular path also show increased activation of the hippocampus (Wolbers et al., 2007). Caloric vestibular stimulation activates the hippocampus in humans (Vitte et al., 1996). Although the head is fixed and thus there are no vestibular signals that are generated or required for this task, the relationship between vestibular function and performance has been examined in several studies (Schautzer et al., 2003; Brandt et al., 2005; Hufner et al., 2007). Patients with bilateral vestibular failure are impaired at finding the hidden platform, but perform as well as matched controls in navigating to the platform when it is visible. Navigation deficits were far more subtle in unilateral vestibular-deficient patients, and only appeared in patients with right, but not left, vestibular failure (Hufner et al., 2007). Structural analyses via magnetic resonance imaging revealed that hippocampal volumes were significantly decreased in bilateral vestibular patients (Brandt et al., 2005), whereas major volumetric reductions in unilateral patients were limited to gray matter reductions in the cerebellum, temporal neocortex, thalamus, and area MT/V5 (Hufner et al., 2009).

Vestibular patients are also impaired in object-based mental transformations, another example of a cognitive task performed with the head immobile and thus in the absence of self-movement cues that would engage the vestibular system (Péruch et al., 2011) The experimental groups were Menière's patients after unilateral vestibular neurectomy, patients with bilateral vestibular damage and normals. One task required mental rotation of 3D-objects and two other tasks involved mental scanning and tested the ability to construct and manipulate mental images with metric properties. The authors reported variations in performance corresponding to the level of vestibular loss. Bilateral vestibular patients often had the worst results. The Menière's patients showed greater deficits early after neurectomy and then gradually compensated. This is of particular interest because it demonstrates a role for vestibular signals in processing metric properties of mental representations, supporting the hypothesis that high level processing is in play.

It is fairly common for vestibular patients to have difficulty detecting and estimating the magnitude of passive body displacements in the dark. During goal-directed locomotion, these patients usually make errors in executing the desired trajectory (e.g., Borel et al., 2004; Brandt et al., 2005; Cohen and Sangi-Haghpeykar, 2011). Spatial disorientation is even stronger during complex tasks such as reversing the trajectory along a triangular path or finding a shortcut (Péruch et al., 1999, 2005; Glasauer et al., 2002; Guidetti et al., 2007). Péruch et al. (1999) found that unilateral vestibular loss impairs the orientation component (estimation of the angular displacements) of navigation. The distance component (estimation of the linear displacements) of the spatial representation is also impaired, although to a lesser extent.

Self-motion or optic field flow in the opposite direction can elicit comparable perceptual, motor, and neurophysiological responses. Convergence of visual field flow and vestibular inputs have been observed in many structures including the vestibular nuclei (Xerri et al., 1988), vestibular area 2v (Büttner and Buettner, 1978) and the parieto-insular vestibular cortex (Grüsser et al., 1990).

Hanes and McCollum (2006) identified cognitive deficits associated with vestibular dysfunction including short-term memory, concentration, arithmetic, and reading. For example, patients with central vestibular lesions required to count backward by twos make more errors and are slower than controls. This was interpreted as resulting from "spatialization" of the task, perhaps in terms of number line representation. Performance impairments can be categorized as direct, that is, tasks that implicitly or explicitly require using information about the 3D structure of space and movements (such as navigation and spatial memory). This also includes the use of spatial strategies in non-spatial domains. Of particular interest here is that a common strategy of skilled mnemonists is to employ mental imagery of places and signs to situate information to be memorized. It would then follow that spatial cognitive deficits could limit the capacities of patients for this type of memorization skill.

Indirect effects of vestibular deficits on cognition derive from the greater demand on attentional and cognitive processing resources at the expense of other ongoing activities (Smith et al., 2005b). For example, the lack of vestibular information requires the sometimes effortful substitution of visual, proprioceptive, and other signals in order to maintain balance, posture, and gaze. Visuospatial processing is also more difficult. This reduces attention, limits concentration and could tie up mental processing resources, impairing other activities such as multi-tasking, processing sequences, and attention-shifting. Patients could thus have difficulty organizing multiple sources of information, in particular integrating new information while retaining previous items in memory – this could impair problem solving and conflict resolution. All of these are important for spatial orientation and navigation. For example, routes are often schematized in terms of sequences of intermediate goals and the associated trajectories to be followed to the next intermediate goal.

Note also that vestibular deficits often report sensations such as vertigo, disorientation, discomfort with repeated peripheral patterns during movement, etc. These then are associated with psychiatric problems such as agoraphobia (such environments provide troubling cue conflicts), excessive fatigue, depression, and anxiety. Overall, these all can lead to indirect negative impacts on measures of spatial and non-spatial cognitive processing.

PROCESSING OF VESTIBULAR SIGNALS FOR SPATIAL REPRESENTATIONS IN THE HIPPOCAMPAL SYSTEM

Head direction (HD) cells fire when the head of the rat (or mouse, or chinchilla) is oriented in a particular direction in the yaw plane, regardless of its position in the environment (Ranck, 1986; Taube et al., 1990; Muir et al., 2009; Yoder and Taube, 2009). HD responses are found in all of the brain areas designated as the Papez circuit, running from the brainstem to the hippocampus. The signals are generated in the brainstem lateral mammillary nucleus and dorsal tegmental nucleus (DTN) of Guddens which receives inputs from the vestibular nuclei (Bassett and Taube, 2005). Although the direction responses are anchored by background visual cues (likely distinguished by motion parallax; Zugaro et al., 2001) and are influenced by optic flow stimuli (Arleo et al., 2013), they remain selective for direction in darkness (e.g., Yoder and Taube, 2009). Stackman and Taube (1997) injected sodium arsanilate in the vestibular end-organs of rats, and this abolished the directional responses in the anterodorsal thalamus. Yoder and Taube (2009) studied HD cells in a mouse strain with nearly complete absence of otoconia and hence minimal otolith function. HD cells were observed but signals were more weakly controlled by visual landmark cues, and responses degraded over successive trials and were unstable in darkness.

Principal neurons of the hippocampus discharge selectively as the rat, mouse, or human occupies a particular position in its real or virtual environment (O'Keefe and Dostrovsky, 1971; Ekstrom et al., 2003; Chen et al., 2013). This activity is considered to participate in an internal representation of the environment (O'Keefe and Nadel, 1978). Indeed, during immobile pauses prior to locomotion, these cells fire in rapid sequences corresponding to the imminent trajectory the rat is about to take (Pfeiffer and Foster, 2013). Vestibular lesions suppress these place responses (Stackman et al., 2002; Russell et al., 2003a) and cause other changes in hippocampal physiology (Smith et al., 2005a; Russell et al., 2006). Furthermore, rats with hippocampal lesions are impaired in orienting to a goal after being passively rotated (Mathews et al., 1989) and in spatial learning (Russell et al., 2003b).

Place learning in the Morris water task critically depends upon intact circuitry upstream of the vestibular organs leading to hippocampus (and involved in the generation of HD cell signals; Vann et al., 2003; Clark and Taube, 2009; Clark et al., 2013) as well as the hippocampus itself and related structures (Morris et al., 1982; Sutherland et al., 1982). These patterns of damage can leave other forms of navigation, such as cued navigation, unimpaired.

Comparisons of place responses in hippocampal neurons of rats before and after rotation of the experimental arena in darkness revealed that a subset of neurons maintained their firing fields at the same position in absolute space, rather than rotating with the apparatus (Wiener et al., 1995). This was interpreted to indicate that the brain had detected the angle of rotation, perhaps via the horizontal semicircular canals, then compensated for it by stabilizing the hippocampal position representation. Since proprioceptive cues may have also played a role in this, a new experiment was devised where the head of the rat was immobilized, its body suspended in a hammock (with the leg protruding through holes), and passively displaced on a mobile robot (Gavrilov et al., 1998). Hippocampal place responses were recorded under light conditions, and they persisted in complete darkness. This provided further, and more direct support for vestibular updating of hippocampal spatial representations. In this same experimental protocol, passive rotations in the dark synchronized hippocampal local field potentials to rhythmically oscillate at 8 Hz, the "theta" rhythm, which is associated with locomotion and active exploration (Gavrilov et al., 1996).

During locomotion in an open field, hippocampal responses in a given place are the same regardless of the orientation of the head, and hence the view perceived by the rat, which is a form of abstraction (Wiener, 1996). This suggests that there is a memory process associating the successive multiple views to produce the same cellular response, presumably reflecting a single coherent representation. One way for the brain to detect that the head is in a certain place would be to compute the distances and angular headings of at least two environmental landmarks. This would require simultaneous storage and comparison of this information, implicating working memory and multi-tasking, processes associated with the hippocampal–prefrontal cortex pathway. Since vestibular lesions abolish place cell activity and induce hippocampal atrophy, perhaps these losses could also impair these processes as well as affecting memory in spatial and non-spatial domains as observed after hippocampal lesions.

Grid cells of the entorhinal cortex (situated in the pathway from the HD system to the hippocampus) discharge as a rat occupies places that are distributed along the nodes of a hexagonal grid within its environment (Moser et al., 2008). Thus these neurons provide a coordinate reference frame for navigation. No study has yet tested the effects of vestibular lesions on grid cells. However, computational models of grid cells require head orientation input – and HD cells are also found in entorhinal cortex. This, and the additional computational requirement for self-displacement signals, indicates that vestibular signals would also be required for grid cell activity.

If vestibular-deficient patients do not have place, HD or grid responses in their hippocampal system, this would deprive them of valuable spatial signal processing and representation capacities. Furthermore, the absence of these signals during development could impair the construction of circuits underlying orientation and navigation behaviors, and perhaps other cognitive functions that these areas contribute to as well. Indeed, eventual hippocampus mis-wiring in the absence of vestibular inputs could also have an impact on non-spatial cognitive processing (Wiener, 1996) by this structure as well and on signaling to downstream structures like prefrontal cortex and ventral striatum.

DEVELOPMENT OF BRAIN REPRESENTATIONS OF THE ENVIRONMENT AND ORIENTATION CAPACITIES IN RATS

During the first few weeks of postnatal life the navigational capacities of the rat and other rodents develops rapidly. Rat pups first venture out of the nest around postnatal days (PD) 10–11 (Bolles and Woods, 1964) and rapidly increase explorations there around PD 16–19 (Alberts and Leimbach, 1980). (Rat pups first open their eyes on PD 15, the same age that they start to walk while bearing the body weight). These exploratory trips appear to be directed not only by internal motivational cues and biologically significant proximal cues (e.g., heat sources) but also to acquire information about distal visual cues (Loewen et al., 2005). During this period the circuitry of the hippocampus and related structures also undergo significant structural and functional development (Bachevalier and Beauregard, 1993; Dumas, 2005). It is generally believed that maturation of the hippocampus is delayed compared to other brain regions, rendering rats incapable of performing hippocampal dependent tasks until at least PD 19–25 (Bachevalier and Beauregard, 1993; Stanton, 2000; Dumas, 2005). A growing body of data from studies investigating the ability of young rats to navigate, however, suggests that the neural systems involved in navigation may be functional even earlier than this. Of particular interest are studies examining the ontogeny of spatial firing characteristics of neurons in the hippocampus and related brain regions implicated in spatial navigation and memory. Langston et al. (2010) reported that the activity of HD cells in the pre- or parasubiculum of preweanling rats displayed adult-like properties at PD 15–16 and the proportion of HD cells was similar to that of the adult animal. Although hippocampal place cells displayed spatially selective firing and medial entorhinal grid cells displayed their characteristic spatially periodic firing shortly thereafter (PD 16–18), the spatial firing patterns of these cells either continued to become more precise and mature and the proportion of responsive cells continued to increase toward adult levels over the next 10–17 days (Langston et al., 2010; but see Wills et al., 2010, 2012). Overall, these observations suggest a primacy of directional processing by HD cells, which is followed by the maturation of place and grid cell signals, respectively (Ainge and Langston, 2012). If hippocampal place cells and the directional tuning observed in some grid cells depend upon HD cells (Knierim and Hamilton, 2011), it is perhaps not surprising that HD cells also mature earlier. These considerations would lead to the expectation that behaviors guided by orientation signals provided HD cells should emerge earlier in development than more complicated cognitive functions such as place navigation (Ainge and Langston, 2012).

Akers et al. (2011) adapted the Morris water task in order to develop a more sensitive assessment of control of navigation by distal visual cues. Prior work from this group examined the effects of translating the pool to another overlapping position in the room with salient visual cues on the walls (i.e., shifting it within the distal cue reference frame). The rats were first trained to navigate to a hidden platform, the pool was displaced in the room, and the rats could swim either to the same precise location in the room where the platform was previously located or to navigate toward the previous location relative to the pool border, respecting its orientation relative to the room cues (Hamilton et al., 2007, 2008, 2009). The rats chose the latter, suggesting that the distal cues can be engaged for orientation information while precise spatial location is based on the local frame of reference (the pool border). The possible outcomes of the translation test described above were recently dissociated by Stackman et al. (2012) in the mouse. Following training these authors pharmacologically inactivated either the anterodorsal thalamus or CA1 subfield of the hippocampus prior to the translation test. Mice with CA1 inactivation navigated to the relative location relative to the pool, whereas mice with thalamic inactivation preferred the location in the room, supporting the contention that navigation based on orientation relative to distal room cues depends on thalamic HD cells.

Hamilton et al. (2007) also trained rats to navigate to a cued platform (i.e., marked by a conspicuous visual cues) in the same distal room environment as used in the hidden platform task. After the rats mastered performance the pool was translated while the cued platform either remained in the same location relative to the room cues or the same location relative to the pool border. The rats

succeeded at the latter, but surprisingly, when the cued platform was placed in the same precise location relative to the room cues, but in a different part of the pool, the rats first navigated in the direction of the platform's previous position relative to the pool walls (respecting the orientation of the room) before correcting course to the cued platform. Thus they initially ignored the cues co-localized with the platform, and instead relied on the pool border in relation to the room orientation, suggesting a priority for this type of navigation strategy at the expense of beacon utilization. These observations provide further evidence that distal cues can control orientation independently of processes that would determine precise spatial localization, and are consistent with previous work by the same group showing that the initial orientation of swim trajectories to a cued platform in the water task are controlled by distal room cues, whereas the proximal cue co-localized with the platform guided subsequent navigation (Hamilton et al., 2004). Interestingly, this dissociation was hinted at by the fact that rats tended to engage in head-scanning behavior after navigating a short distance from the release point. Further manipulations such as changing room cues or relocating the cued platform revealed that these head-scanning behaviors marked the transition between control by distal room cues and control by the proximal cue.

Recently, Clark et al. (2013) demonstrated that lesions of the DTN (part of the brainstem circuit processing vestibular signals to generate HD cell activity) dramatically impair the engagement of distal cues in this Morris water task. Using the cued navigation task described above these authors demonstrated that rats with DTN lesions directly to the cued platform regardless of its position in the room and pool during the translation test. Akers et al. (2011) also utilized this variant of the task to examine the developmental trajectory of orientation control by distal cues. Interestingly, rats at PD 16 showed no significant difference in latencies to the cued platform whether it was in the same location in the pool or room, whereas all rats PD 17 or older displayed the adult pattern of outcomes, first erroneously swimming to the previous position relative to the pool walls, as guided by its orientation relative to the room. Most studies indicate that the emergence of place navigation in rats begins between PD 20–22 (review: Akers and Hamilton, 2007) which is generally taken to reflect the maturation of the hippocampus, supported by upstream sensory and cognitive systems involved in navigation. The observations of Akers et al. (2011) are consistent with the hypothesis that distal cues control orientation, but not precise position, very early in development, at the same time that HD cells are maturing functionally, prior to the appearance of mature place cell and grid cell responses.

HIPPOCAMPAL DEVELOPMENT IN CHILDREN

Knickmeyer et al. (2008) reported a 13% increase of hippocampal volume from the ages of 1 to 2 years (but relatively little growth could be seen after it was normalized for total brain volume). Giedd et al. (1996) found that right hippocampus growth (normalized with respect to cerebral volume) correlated with age only in females, and that the left hippocampus did not increase with age between 4 to 18 years in males, or females. Uematsu et al. (2012) employed a cubic regression to chart the developmental trajectories of hippocampal regions. Their data show increases in hippocampal volume during the first 6–7 years of life, with a peak at about the age of 10–11. Gogtay et al. (2006) performed a volumetric study of MRI scans from humans aged from 4 to 25. They observed that total hippocampal volume does not change over this period although there are regional variations. Concerning connectivity, Ábrahám et al. (2010) showed that myelination progresses differently in hippocampal subregions, reaching adult levels in fimbria-fornix, stratum lacunosum-moleculare and alveus at 3 years of age, stratum radiatum of CA3 and all of stratum oriens at 8 years, but not the stratum radiatum of CA1, pyramidal cell layer of all subregions and the hilus. Even at the age of 11, myelinization was not complete in the hilus. An adult-like pattern of calbindin immunoreactivity can be observed at 11 years of age.

All of these data show periods when growth is taking place and is completed, but do not reveal when the networks are functional, which may occur somewhere within these periods. Even if a particular network arrives at maturity in the absence of vestibular inputs, the hippocampus is a highly plastic structure and would be expected to integrate substitutive inputs easily. However, the hippocampal atrophy in adult neurectomy patients would suggest that the absence of vestibular input in childhood would also impair hippocampal development. This could have different impacts at the respective ages. The data presented above suggests that different types of growth and maturation are occurring in the periods up to age 2–3, then leading up to 6–8, and then up to the age of 11 where adult-like characteristics appear.

ONTOGENESIS OF SPATIAL NAVIGATION AND ORIENTATION IN CHILDREN

Several laboratories have examined the development of place navigation and related processes in young children, controlling and distinguishing from other simpler behaviors such as cued navigation. Lehnung et al. (1998) tested children in a 3.6-m diameter circular area closed off with curtains. Under dim lighting conditions, points on the floor were marked with lit fiberglass wires. The child had to first explore the group of points to find those selected as rewarded sites for that day, and then return and find them again. Both proximal cues on the floor (teddy bear, etc.) and wall cues were present. Various controls and experimental conditions were tested. While 5-year-olds employed the proximal cues, the 10-year-olds were able to use distal or proximal cues for orientation. Seven-year-olds were at a transition point, where half used only proximal cues, while the other half could use both cue types.

Overman et al. (1996) tested children in large real world environments, including a radial arm maze, a "dry Morris water maze" 0.9 m high and 3.6 m in diameter filled with plastic packing chips and a large 61 m circle in an outdoor playing field. In the radial arm maze, where each arm was rewarded only once per trial, children under 5 years old were impaired in both cued and non-cued versions when eight arms were used, showing spatial working memory performance inferior to older children and adults. (With only four arms open in the maze, these children succeeded at performing at adult levels however). When confronted with four forced choice trials, then, after a short delay, they were required to go to the remaining arms, the children under 5 years old performed at chance levels, 6- to 10-year-olds performed better, but only 20% of the latter achieved adult performance in this place learning task.

In the dry Morris water maze, performance in finding the hidden "treasure chest" progressively improved among subjects until the age of 7 years. And only those children above the age of 8 years could localize the reward on a scale model of the maze. In the field the subjects were shown a goal location, blindfolded and driven along a circuitous route inside the circle, then asked to return to it. Performance improved in children 7 years and above, with 9-year-olds and older performing as well as adults. This is consistent with observations that 10-year-old children can resolve large-scale navigation tasks, but not 3- to 4-year-olds (Acredolo, 1976).

Virtual navigation tasks were developed as analogs of behavioral protocols used with rodents, and it is notable that many aspects of control of these tasks by spatial and non-spatial cues are similar across species. In cue competition experiments rats and humans display similar patterns of responses to removal of distal visual cues (e.g., Hamilton and Sutherland, 1999; Redhead and Hamilton, 2009). When the local apparatus is displaced in the same room after training both animal and human virtual navigation experiments suggest that distal cues control the directionality of navigation within the local apparatus (i.e., the pool). This too provides evidence for a fundamental similarity in how distal cues control navigation in the respective tasks. Thus it has been argued that parallel studies in humans and non-human animals could provide important information at multiple levels of analysis about the neurobehavioral relationships involved in place navigation and the development of these relationships. Interestingly, there are notable parallels in the development of spatial navigation abilities in rodents and humans in the respective tasks. Using a VMWT, Hoesing et al. (2000) found that children younger than age 7 did not reliably use a place navigation strategy to solve the VMWT but rather relied on various types of other strategies (e.g., circling a particular distance from the pool wall until the platform was encountered, randomly searching the pool). However, the pattern of successful performance by prepubertal children above age 7 (Hoesing et al., 2000) and post-pubertal adolescents (Hamilton et al., 2003) are comparable to that observed in adults (e.g., Hamilton et al., 2009) in that they learn to execute direct trajectories from multiple release points and persisted in searching at the target location during a probe trial with no escape platform.

Newcombe et al. (1998) found that from the age of 22 months, infants benefit from the use of the relations between distal cues to find a toy they had seen buried in a sand box. The children's gaze at the site was interrupted and they started searching from a different point on the periphery. Ribordy et al. (2013) studied children aged from 2 to 5 years searching for rewards beneath an array of cups distributed in an open field arena 4 m × 4 m surrounded by opaque plastic walls on three sides. At 25–39 months of age, the infants could locate one rewarded cup out of the four presented (a simplified version of the task), albeit in the absence of local cues. However, 18- to 23-month-old infants were incapable of this. Thus both studies concur that near the age of 2 years capacities emerge for localization relative to distal cue configurations. Ribordy et al. (2013) point out that the age of 2 also marks the beginning of autobiographical memory as well as when the hippocampus reaches a certain state of maturity.

In summary, these studies suggest that there are at least two periods in development when new spatial skills appear. At the age of 2, infants are capable of rudimentary spatial localization (Ribordy et al., 2013), while capacity for place navigation emerges around 6–7 years of age in the Overman et al. (1996) and Hoesing et al. (2000) studies, and at the age of 11, adult performance appears. This is remarkably concordant with the three ages which mark milestones in hippocampal volume increase and myelination as noted in the previous section. Nevertheless, the interpretation of the coincidences of crucial ages in these developmental studies is clouded by the occurrence of other interrelated events at these ages. For example, at the age of 2, infants have recently gained mastery of independent walking and exploration, and this too might help elaborate spatial representations and promote hippocampal development.

Further advances could be made measuring performance in specific types of navigational processing using virtual environments such as the VMWT. Manipulations such as the combined cued navigation and pool translation in the VMWT permit to distinguish different ways of using distal visual cues for orientation alone or precise localization – processes that may be differentially affected by loss of vestibular function before or after key ages. Thus such approaches may prove useful in characterizing the effects of damage to the vestibular system on subsequent development of spatial navigation abilities. Importantly, because tasks of this type are administered via a computer program and interface experimental conditions can be controlled precisely, and can also be easily coupled with measures of functional brain activity (Cornwell et al., 2008), they will likely play an important role in further advancing our understanding of the behavioral consequences of early vestibular damage and their neurobiological bases.

CRITICAL PERIODS

Rieser et al. (1986) compared sighted with blind adults who had lost vision early or late in life and had similar performance in evaluating perspective from an imaginary new observation point. When subjects walked without vision to the new point, pointing performance improved in the sighted and late-blinded subjects but not those of the early-blinded subjects. This suggests that early absence of vision leads to different types of representations of space. While there is a great variety in the performance levels of early blind vs late blind subjects, there seems to be a tendency for the former to employ route strategies while the latter engage mapping for navigation tasks (Thinus-Blanc and Gaunet, 1997).

The concept of critical period has been well developed for visual system ontogenesis (Imbert and Buisseret, 1975). Since multiple brain systems are respectively implicated in complementary orientation and navigational processing and they mature at different times, accurate vestibular signals at these times would be necessary for timely development. Critical periods for vestibular inputs would thus exist for each respective type of spatial processing.

POSSIBLE MECHANISMS FOR VESTIBULAR DEFICITS LEADING TO COGNITIVE IMPAIRMENTS

Vestibular deficits could lead to diverse and distinct types of problems in cognitive processing problems with different respective

underlying mechanisms. We showed (Wiener-Vacher et al., 2012b) that posturomotor control is delayed after a sudden complete vestibular loss due to meningitis before the age of independent walking. This led to long-lasting posturomotor instability in the absence of any neurological impairment. We suggested that the oscillopsia resulting from a complete lack of vestibular information in these children leads to dynamic and head–trunk instability. This could then contribute to secondary delays in learning processes (reading, writing, fine motor control) as well as building coherent representations of the body as well as its position relative to surrounding space. Much remains to be learned about the impact of complete or partial vestibular loss at different ages in children on the development posturomotor and fine motor control, oculomotor control in cognitive activities (reading, writing), spatial orientation, and body representation.

The absence of vestibular inputs to the hippocampus would lead to failure to establish normal brain representations of the body in space. A consequence of this would be difficulties in understanding spatial relations of environmental features. However, the resulting hippocampal atrophy could have a negative impact on other processes as well, like memory, context-dependent behaviors and relational reasoning. Another problem would derive from vestibular impairments leading to incomplete and imprecise sensorimotor feedback loops of many varieties. This would not be limited to activities involving head movements, since head immobility would be detected with lower certainty too. During development infants make myriad movements, and when the brain detects their outcomes, it can make corrections to refine sensorimotor coordination and build representations. Objects in three-dimensional space are understood not simply by their visual profile, but by how they feel, how they change appearance when manually rotated or when one walks around them, their weight, inertial and dynamic properties. Vestibular-impaired children's problems with the gravity sense, the sense of orientation, awareness of the relations among one's body parts and the distinction of self-movement from object movement could lead to impairments in their acquisition of knowledge through such sensorimotor feedback and interactive behavior. Another type of problem is related to absent or incomplete gravitational information which can lead not only to balance problems, but also to inaccurate compensation for gravitational forces on the body parts and environmental objects, particularly during movement. It has been demonstrated that the brain elaborates models of visually observed movement dynamics that distinguish those modulated by gravitational force (i.e., linear acceleration at 9.8 m/s^2) from others (Zago and Lacquaniti, 2005). Other cognitive representations may also be built up from cerebral simulation of concordant sensorimotor loop activation experience, for example, mentally replaying walking through an environment could help build brain representations of that environment. Whether such experience is limited by choice (by a child who moves about and explores less frequently and less freely to avoid instable or disturbing situations) or by the incomplete nature of the sensory return information, this would nonetheless lead to poor spatial representations. Other sensory inputs can also be compromised in cases of vestibular deficits. For example, unstable gaze (in particular patients with spontaneous nystagmus) would impair visual perception and hence visual feedback from movements. Again the failure to distinguish visual field movements due to self or environmental features could have dramatic consequences. Many vestibular patients also suffer from partial or complete auditory deficits, which would impair access to echoes and ambient sound which also provide information about position and environmental structure.

CONCLUSION

Our hypothesis is that an absence of vestibular information early in life can lead to reduced cognitive performance in several domains, as well as altered spatial cognitive representations (compared to children with no such vestibular deficit). This would persist a long time after vestibular compensation in the absence of appropriate therapy. The argument can be summarized as follows: the importance of the hippocampal system in spatial and other cognitive processing is supported by a vast experimental and neurological literature. Particularly striking evidence comes from neurophysiological recordings of place cell, HD cell and grid activity in rodents, activation of the hippocampus during virtual navigation in humans, and others. Theoretical arguments were advanced here for the roles of vestibular signals in building spatial reference frames and updating spatial representations. This is motivated by the observations that vestibular inactivation leads to the loss of HD and place cell activities as well as hippocampal atrophy and navigation deficits. Finally, the data on the ontogenesis of navigation behavior and hippocampal development converged remarkably on milestones at the ages of 2, 7, and 11. This leads to a refinement of our hypothesis wherein the onset of vestibular dysfunction prior to these milestones will delay the normal development of corresponding cognitive functions, and possibly lead to specific period-dependent changes in hippocampal structure and function. These may prove difficult to detect behaviorally because of rapid compensation of partial vestibular deficits, the high degree of plasticity that characterizes the hippocampal system, and variability among patients in their experiences learning to substitute other sensory modalities for the missing vestibular inputs. Nonetheless we predict that specific cognitive deficits will be detectable in at least a subpopulation of patients who lost vestibular function prior to the respective ages of 2, 7, and 11. One interesting question concerns the respective contributions of otolith and semicircular canal inputs for achieving these milestones. This knowledge would then lead to adapted therapies to help recover from these deficits.

In general, the issue of cognitive impact of deprivation of vestibular signal in children should have important consequences in patient care. Screening for vestibular loss should be done routinely in deaf children or in children with psychomotor developmental delays, who are often misdiagnosed as neurologically impaired or "slow." Every effort should be made to avoid aggravating vestibular loss, for example, detect residual vestibular function prior to cochlear implantation in young patients and planning surgeries accordingly (Jacot et al., 2009). It is important to control for the possible effects of hearing impairment that are often associated with vestibular deficits. For example, vestibular deficits may impact on reading performance and further compromise language skills beyond impairments due to hearing loss. These

screening tests must be comprehensive, including otolith testing which can now be performed easily, reliably, and relatively inexpensively via vestibular evoked myogenic potentials (VEMP; Jacot and Wiener-Vacher, 2008). While the caloric test remains a staple of the vestibulometry clinical battery, it is insensitive to otolith function, which we argue to be essential for establishing spatial reference frames.

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AUTHOR CONTRIBUTIONS

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Caloric vestibular stimulation in aphasic syndrome

David Wilkinson[1] *, Rachael Morris[1], William Milberg[2] and Mohamed Sakel[3]

[1] School of Psychology, University of Kent, Canterbury, Kent, UK
[2] Department of Psychiatry, Harvard Medical School, Boston, MA, USA
[3] East Kent Neuro-Rehabilitation Service, East Kent Hospitals University NHS Foundation Trust, Kent, UK

Edited by:
Paul Smith, University of Otago Medical School, New Zealand

Reviewed by:
Claudio V. Mello, Oregon Health and Science University, USA
Paul Smith, University of Otago Medical School, New Zealand
Stephane Besnard, INSERM U1075, France

***Correspondence:**
David Wilkinson, School of Psychology, University of Kent, Canterbury, Kent CT2 7NP, UK
e-mail: dtw@kent.ac.uk

Caloric vestibular stimulation (CVS) is commonly used to diagnose brainstem disorder but its therapeutic application is much less established. Based on the finding that CVS increases blood flow to brain structures associated with language and communication, we assessed whether the procedure has potential to relieve symptoms of post-stroke aphasia. Three participants, each presenting with chronic, unilateral lesions to the left hemisphere, were administered daily CVS for four consecutive weeks. Relative to their pre-treatment baseline scores, two of the three participants showed significant improvement on both picture and responsive naming at immediate and 1-week follow-up. One of these participants also showed improved sentence repetition, and another showed improved auditory word discrimination. No adverse reactions were reported. These data provide the first, albeit tentative, evidence that CVS may relieve expressive and receptive symptoms of aphasia. A larger, sham-controlled study is now needed to further assess efficacy.

Keywords: neuro-stimulation, stroke, language, communication, rehabilitation

INTRODUCTION

Aphasia is a language disorder most commonly caused by stroke to the left cerebral hemisphere in right-handed adults (Hamilton et al., 2011). The condition often disrupts comprehension, speech, reading, and writing, and impacts general rehabilitative outcome (Code and Herrmann, 2003; Paolucci et al., 2005; Hilari, 2011). Aphasia affects approximately 38% of patients who suffer a left hemisphere stroke, persisting in approximately 40–60% of cases (Meinzer et al., 2005). Unfortunately, the conventional treatment of speech and language therapy is often not effective, especially in chronic cases (Robey, 1994; Berthier, 2005; Kelly et al., 2010; Brady et al., 2012). Preliminary success in relieving certain symptoms of aphasia has, however, been achieved using transcranial direct current stimulation and transcranial magnetic stimulation (e.g., Naeser et al., 2005b; You et al., 2011). Here we investigated the potential efficacy of another form of non-invasive neuro-modulation, caloric vestibular stimulation (CVS).

Caloric vestibular stimulation involves the transmission of either warm or cool temperature, usually via water or air, from the external ear canal to the vestibular organs located in the adjacent labyrinth. These temperatures alter the density of endolymphatic fluid within the semi-circular canals and otolith organs, which in turn modulates the firing rates of vestibular hair cells. The resulting change in vestibular nerve activity is interpreted by the brain as a natural head movement, and increases blood flow across many cortical regions including language areas 44/45 (Broca's) and 22 (Wernicke's) (Fasold et al., 2002; Dieterich et al., 2003). These flow changes may be important because there is evidence from brain-injured patients that they correlate with spontaneous improvements in repetition and comprehension (Muira et al., 1999; Heiss and Thiel, 2006; Hamilton et al., 2011). Vestibular stimulation also modulates the release of glutamate (Horii et al., 1994; Holstein et al., 2012), nor-adrenaline (Nishiike et al., 2001), serotonin (Ma et al., 2007), and acetylcholine (Horii et al., 1994), all of which have been implicated in cognitive function and recovery (Klein and Albert, 2004).

A small number of studies have monitored language ability during CVS. Magrun et al. (1981) reported spontaneous improvement in the speech of developmentally delayed children following 5, 10 min CVS sessions. Schiff and Pulver (1999) reported a case of acute aphasia in whom brief language improvement occurred shortly after a single session of CVS of unspecified duration. This patient presented with severe expressive difficulties, but following CVS was briefly able to produce full sentences using appropriate emotion and intonation. By contrast, Vallar et al. (1995) described another case in which CVS did not improve language. However, this observation was based on 1 min sessions of CVS which are much shorter than the durations used in neurostimulation studies that have reported favorable language outcomes (Naeser et al., 2005b; Baker et al., 2010). Recently, for example, Barwood et al. (2012) applied low frequency repetitive transcranial magnetic stimulation (rTMS) to the right homolog of the pars triangularis of Broca's area (BA 45) for 20 min per day and found a subsequent improvement in picture naming, repetition, and auditory comprehension (for similar outcomes using rTMS, see Naeser et al., 2005a,b; Hamilton et al., 2010). In a similar vein, You et al. (2011) showed improved auditory comprehension and spontaneous speech following repeated 30 min administrations of cathodal transcranial direct current stimulation (tDCS) to the right homolog of Wernicke's area (for a similar outcome using tDCS, see Kang et al., 2011).

Compared to CVS, however, TMS and tDCS have several shortcomings that limit their rehabilitative potential. Firstly, both techniques involve the stimulation of a specific brain area which requires *a priori* knowledge of where to position the magnetic coil/electrodes. This can be particularly difficult when working

with stroke patients whose functional anatomy is often altered by the presence of a lesion (Bolognini et al., 2009). TMS is also associated with an increased risk of seizure and is difficult to miniaturize, while tDCS is contraindicated for individuals with electronic implants or certain types of metal plates (Rossi et al., 2009).

The traditional method of CVS involves irrigating the external ear canal with ice-cold water. It is difficult to control the temperature and rate of flow during irrigation, and perhaps, more important, the presence of cold water in the external ear canal induces vertigo, a strong horizontal nystagmus and nausea. Advances in biomedical engineering have, however, led to the development of a solid state device that can warm or cool the external ear canal via a small thermal-electric probe. The temperature can be easily maintained a few degrees above 15°C which is the approximate point at which the vestibular nerves reach asymptote (Reker, 1977). Importantly, this temperature range is not associated with nausea, marked nystagmus or vertigo. An added benefit of solid-state devices is that they can be made highly portable and easy to use, so are suitable for home-based, self-administration.

The aim of the current study was to seek preliminary evidence for the hypothesis that the administration of CVS can result in measurable improvements in language function in patients with aphasia. We recruited three individuals in the sub-acute/chronic phase (i.e., >6 months post-onset) of stroke who were suffering from receptive and expressive aphasia. All had shown either little or no improvement in language ability within the preceding 3 months. Each individual received 20 days of CVS, with each daily session lasting 20 mins. Language and communication was assessed using subtests of the Boston Diagnostic Aphasia Examination (BDAE; Goodglass et al., 2001) which were administered across two baseline sessions, on the final day of stimulation, and then at 1 and 4 weeks post-stimulation. We did not include a sham condition because we felt it unreasonable at such an early stage of study to ask brain-injured patients to travel to the clinic every day for 4 weeks with no realistic prospect of gain. Given the failure of many speech and language rehabilitation programs, we felt it more appropriate to first establish whether any of our participants actually showed improvement, and for how long. Once the wash-out period had been estimated, a subsequent study could implement a cross-over design that exposed all participants to appropriately spaced active and sham treatments.

CASE HISTORIES

Three right-handed aphasic individuals were recruited via physician referral from the Kent and Canterbury Hospital, East Kent Hospitals University NHS Foundation Trust. All participants had suffered an ischemic stroke at least 6 months prior to study enrolment, and had received speech and language therapy during the acute phase. Given the exploratory nature of the study, participants were only excluded if they had not suffered a left, unilateral stroke, had a significant history of neurological or medical illness, or presented with inner ear pathology or hearing difficulties.

Participant 001, a 62-year-old female, was admitted to hospital following a left middle cerebral artery (MCA) infarct, 11 months prior to study enrolment. CT investigation at admission indicated a large area of ischemic damage within the territory of the left MCA, with additional involvement of the caudate nucleus (see **Figure 1A**). A supplementary MRI investigation 4 months post-injury showed evidence of a prior hemorrhage most noticeably affecting segments M2 and M5 of the left MCA and the lenticular nucleus. The results were suggestive of persisting stenosis in the left sylvian artery at segment M2 of the MCA.

Participant 001 presented with right hemiplegia, requiring the use of a wheelchair except for short, indoor distances. Although she was able to mobilize over short distances with assistance and the use of a walking stick, she found it difficult to weight-bear fully through either foot, and required help with trunk flexion when transferring from sitting to standing. This was hampered by a right glenohumeral joint subluxation, sequencing difficulties, and an increased muscle tone of right upper and lower limbs.

Speech therapy reports completed soon after admission indicated that 001 showed severe global aphasia affecting all language modalities. At the time of study enrolment, 001 had shown some improvement in receptive communication, though spoken output was limited to single words and short automatic phrases. Repetition was also moderately impaired; 001 was able to repeat single words well but could not manage short sentences. Progress in speech and physiotherapy had been limited, largely due to 001's complex presentation that also involved low mood, anxiety, and tearfulness.

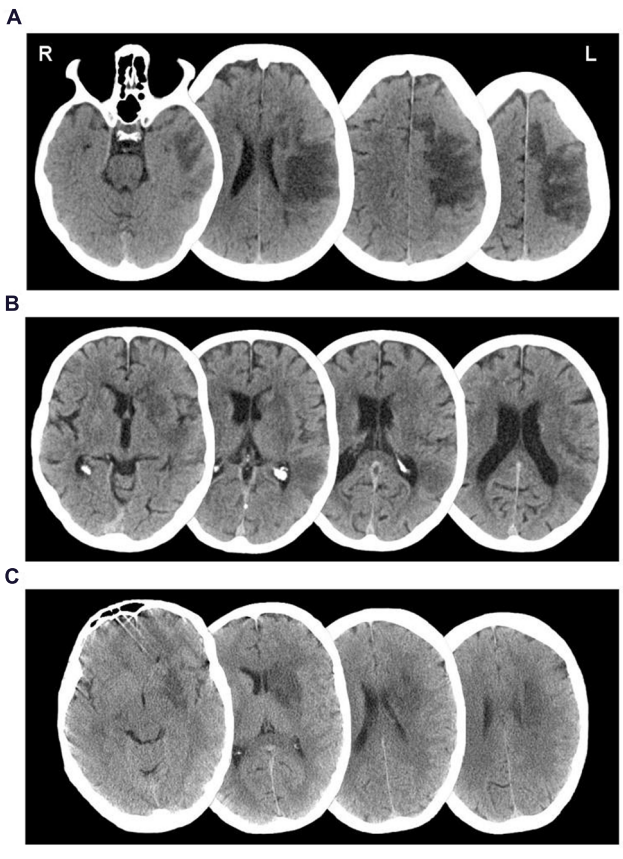


FIGURE 1 | Axial CT imageshowing lesion distributions of participants (A) 001, (B) 002, and (C) 003.

At the time of study enrolment, 001 was living semi-independently in her own home with the support of her husband and carers. Her rehabilitation physician advised that her speech and language ability had been stable for several months. She was still unable to transfer independently and scored 3/5 on the Modified Ashworth Scale (MAS; Bohannon and Smith, 1987) for the right flexor digitorum profundus and flexor digitorum superficialis. Perceptual assessment revealed a mild, right-sided visual hemi-spatial neglect, as assessed by subtests of the Behavioral Inattention Test (Wilson et al., 1987). She also showed a constructional apraxia, scoring within the moderate-severely impaired range for both the copying accuracy and planning elements of the Rey–Osterrieth Complex Figure task (Stern et al., 1999), and failing to progress past the initial trial of the WAIS-R Block Design subtest (Wechsler, 1981).

Participant 002, a 70-year-old male, was admitted to hospital 8 months prior to study enrolment, having suffered a left MCA infarct. A CT investigation revealed low attenuation in the left basal ganglia, left parietal, temporal and frontal lobes, plus sulcal effacement and compression of the anterior horn of the left lateral ventricle (see **Figure 1B**). A carotid Doppler test carried out a month later indicated complete occlusion of the left internal carotid artery.

Participant 002 presented with right hemiplegia, reduced coordination of the right upper limb and reduced balance. At the time of study enrolment, 002 was able to walk short distances with supervision and the use of a walking stick, though required the use of a wheelchair when outdoors and had difficulty mobilizing due to distractions. He showed difficulty with motor planning and sequencing and over-activity into flexion in his right upper limb during functional tasks, though this could be overcome by prompting. Poor scapular control and awareness limited the active range of his right glenohumeral joint.

Speech therapy prior to study enrolment indicated severe expressive aphasia and apraxia of speech. Spontaneous spoken output was largely unintelligible. Repetition was also significantly impaired, even at single word level. Apraxic difficulties were evident in attempts to copy lip and tongue movements and repeat sounds. In addition, 002 presented with moderate receptive difficulties. Participant 002 had regularly expressed frustration and low mood at difficulties during speech therapy sessions. At the time of study enrolment, 002 was living semi-independently at home with the support of his wife and carers. His rehabilitation physician advised that his speech and language ability had been stable for several months. On the Rey–Osterrieth Complex Figure task, participant 002 scored within the low-average range for copying accuracy and below average/mildly impaired for the planning element (Stern et al., 1999). He showed moderate to severe impairment on the WAIS-R Block Design subtest (Wechsler, 1981).

Participant 003, a-51-year old male, was admitted to hospital upon sudden onset of aphasia and right-sided weakness, 22 months prior to study enrolment. A CT scan taken upon admission revealed a low density area in the deep white matter of the left posterior frontal lobe, lateral to the anterior horn of the left ventricle (see **Figure 1C**). An additional MRI scan a week later indicated a hyperdense signal in the left temporal lobe, left basal ganglia, left caudate nucleus, and internal capsule extending into the left semiovale. Magnetic resonance angiography (MRA) indicated complete occlusion of the left MCA and left internal carotid.

Speech assessment prior to discharge from hospital highlighted severe expressive and receptive aphasia. Follow up with the community speech therapist suggested that his comprehension difficulties had mostly resolved following discharge, but spoken output remained limited to occasional words and short phrases. Participant 003 also presented with a mild apraxia of speech. Participant 003's speech presentation had remained stable up until 6 weeks prior to study enrolment, when a period of modest, spontaneous recovery occurred. During this time participant 003 began to say more words and sentences, though overall verbal output still remained limited. 003 further presented with a mild right-sided weakness resulting in restricted upper limb movement and reduced fine motor skills. There was muscle weakness of the right lower limb, although he was completely mobile. He scored 5/5 on the Functional Ambulation Categories (Holden et al., 1984), 4/5 on the MRC muscle power testing (Medical Research Council, 1986), and 1/5 on the MAS (Bohannon and Smith, 1987) for his upper right limb, and 40/40 on the Modified Rivermead Mobility Index (Lennon and Johnson, 2000). Tests of visual construction and lateralised attention were not performed because, unlike participants 001 and 002, there was no mention of these capacities at hospital discharge. At the time of study enrolment, Participant 003 was living largely independently at home with his wife.

LANGUAGE OUTCOME MEASURES

Participants were assessed on various sub-tests of the BDAE third Edition (Goodglass et al., 2001) – see **Table 1**.

TEST SCHEDULE

Favorable ethical approval was gained from the University of Kent Psychology Research Ethics Committee, and all participants gave written, informed consent prior to study.

Baseline assessments were administered 10 and 3 days prior to stimulation to gage pre-treatment language ability. CVS was performed from Monday to Friday for the next 4 weeks, and post-CVS assessments were conducted immediately after the last session and then 1 and 4 weeks later. The language assessments were administered in the following order; auditory comprehension, repetition, naming, connected speech.

STIMULATION

Caloric vestibular stimulation was administered via a custom-built, experimental device that modulates the temperature of small, thermo-electric, solid-state probes inserted into the right and left external ear canals (see **Figure 2**). The probes are mounted on a headset and are too large to enter the bony portion of the canal, resting instead on the outer fleshy portion. The probes are held in place by first ensuring that the headphones are properly seated on the head (which ensures that the probes are seated within the ear canals) and then fastening a velcro head-strap to prevent further movement. Each probe can be warmed/cooled independently depending on whether unilateral or bilateral stimulation is

Table 1 | BDAE outcome measures.

	Sub-test	Description
Naming	BNT short form	Participants are presented with the following pictures and asked to name them: house, comb, toothbrush, octopus, bench, volcano, canoe, beaver, cactus, hammock, stethoscope, unicorn, tripod, sphinx, and palette.
	Responsive naming	Participants are required to answer questions such as "What color is grass?" and "What do we tell the time with?" Two points are given for responses within 5 s, one point for over 5 s.
	Naming in categories	Participants are required to name pictures organized into categories of colors, animals, actions, and tools/implements.
Connected speech	Cookie theft description	Participants are asked to describe a complex scene presented in picture format. They are scored on the longest phrase produced.
Repetition	Single words, non-sense words, sentences	Participants are asked to repeat single words, non-sense words and sentences.
Auditory comprehension	Basic word descrimination	Participants are asked to point to a verbally presented object from a selection of pictures.
	Commands	Participants are asked to follow instructions to, for example, "point to the ceiling and then to the floor." One point is awarded for each component of the command that is completed correctly.
	Complex ideational material	Participants are required to answer yes/no questions about a verbally presented paragraph. Each question consists of two yes/no questions. Both must be answered correctly for one point.

required, and is controlled with a hand-held unit that both powers the headset and allows the laterality, duration, and temperature range to be regulated. Actual earpiece temperature is monitored by an embedded thermistor (in the tip of the earpiece) which serves as the control point in a PID (proportional/integral/derivative) temperature controller designed to control overshoot. The actual recorded temperatures are recorded on an SD card and can be viewed to confirm temperature compliance. The mode of action is identical to that of conventional caloric irrigators in that heat is conducted back and forth between the external auditory canal to the inner ear via the temporal bone. Unlike caloric irrigators, however, the device allows for physician-defined, time-varying waveform shapes that can be cycled to maximize vestibular response and reduce physiological habituation.

Otoscopic inspection was performed immediately prior to the first session of stimulation to check for excessive cerumen (which may limit temperature transfer) and to confirm that the external ear canal and tympanic membrane were normal in appearance. With the intention of increasing activity in the damaged left hemisphere, CVS was applied to the right ear canal for 30 consecutive days excluding weekends. CVS sessions lasted 20 min during which time probe temperature cycled continuously between 35 and 17°C, achieving approximately eight complete cycles. This gentle transition between warm and cool made the procedure easy to tolerate, and as expected, participants showed no evidence of disorientation or discomfort during stimulation, nodding when asked if the procedure was comfortable. Throughout stimulation, participants sat upright and were



FIGURE 2 | Illustration of the thermo-modulation device comprising two headphone-mounted ear-probes and an AC powered control unit.

not engaged in prolonged conversation or speech or language tasks.

STATISTICAL APPROACH

Ninety five percent confidence intervals were constructed to determine whether changes from baseline were greater than that which could be attributed to natural variation. For each subtest, upper and lower confidence limits were calculated as two standard errors (SE) above and below the baseline scores, respectively, using the equation $SE = SD\sqrt{1 - \rho}$ where ρ refers to Cronbach's alpha and where the SD was derived from the responses of an allied sample containing 85 aphasic and 15 elderly normal participants (Jacobson et al., 1999; Goodglass et al., 2001; Reise and Haviland, 2005). Given that each participant showed little change across the two baseline administrations of each subtest, the two baseline scores were combined to produce a more reliable estimate of language ability (Weller, 2007). Adjusted reliability estimates (ρ) were therefore calculated using the Spearman–Brown Prophecy Formula (see Nunnally, 1967). To reduce the likelihood of mistaking experimentally induced recovery with that which was already occuring, 95% confidence intervals were only calculated for those subtests in which the change between the baseline and post-CVS scores was numerically greater than the change between the two baseline scores.

There were two instances in which an average baseline was not calculated; participant 001's Basic Word Discrimination and participant 003's Responsive Naming. In both instances, there was a significant difference between the two baseline scores (though this was a much smaller difference than was seen between pre and post-CVS). In these cases it was deemed inappropriate to use an average pre-treatment score and therefore 95% confidence intervals were calculated around the higher of the two baseline measures. In these cases, reliability of the original scale, as opposed to the combined scale, was used.

To provide broader insight into wellbeing and functional recovery, written testimonials from participants' relative/carers are presented below alongside the inferential statistics. These testimonials are, of course, anecdotal and subjective, but nevertheless hold corroborative value.

RESULTS

PARTICIPANT 001

Boston Diagnostic Aphasia Exam subtest scores are presented in **Table 2**.

Statistically significant improvements from baseline were observed in naming and comprehension. Reliable changes were observed on the BNT short form at all follow-up sessions, category naming of Tools during the immediate and post-CVS week 1 session, and responsive naming at immediate follow-up. For auditory comprehension, reliable changes were observed in the commands sub-test at all follow-up sessions, and for word discrimination at the immediate and post-week 1 follow-up.

The above improvements are echoed in the testimonial below.

Testimonial 1 provided by a carer of 001

"*As the carer of XX I wish to share some improvements that have been noticed since she received stimulation at Canterbury University. Her speech is much clearer and she speaks with more confidence. She initiates conversation and is able to let her needs be known. She says short sentences (e.g., Can I have a cup of tea, please?), and has been identifying words and pictures. XX now asks to walk and can walk from the lounge to the kitchen and toilet with the aid of a three pronged stick. XX gets up from the wheelchair and gets herself out of bed into the sitting position. Her right vision seems to have improved. She is also more alert and confident and her facial expressions coincide with what she is trying to express. She clearly understands what is being said to her and expresses/shows appropriate empathy.*"

PARTICIPANT 002

Boston Diagnostic Aphasia Exam subtest scores are presented in **Table 3**. No statistically significant changes from baseline were observed.

The following testimonial did, however, highlight some potential change.

Testimonial 2 provided by 002's wife

"*Since XX started the treatment, his walking and standing has improved a lot. Some of his speech has come back like 'goodnight,' 'I am starving,' and 'I will wash-up'.*"

PARTICIPANT 003

Boston Diagnostic Aphasia Exam subtest scores are presented in **Table 4**. Statistically significant improvements from baseline were observed on the BNT short form at immediate and week 4 follow-up, on category naming of actions at immediate and week 1 follow-up, and for animals at immediate follow-up. Responsive naming also improved at immediate and week 1 follow-up, and sentence repetition improved at all follow-up sessions.

The above improvements are echoed in the testimonial provided by 003's wife.

Testimonial 3 provided by 003's wife

"*Since XX started this trial on 13th May 2013, there has been a marked improvement in his speech. Many people (friends or family) over the phone or face to face, whether they see him on a regular basis or from time to time, have noticed a difference in him during this trial period. I feel that maybe a month/6 weeks before the trial began there was a change happening in XX's speech, but definitely during the trial things have got better. He's coming out with short sentences and although it's a struggle sometimes, he gets there in the end. Something else I feel I should mention is two of XX's speech therapists paid him a visit on 29th May and they both noticed a marked improvement in his speech, after one of them not seeing him for a few months and the other not seeing him for 3 weeks! To sum up, on the whole, XX is definitely speaking more, making a conscious effort to try to make sentences, and I think a little more confident!*"

DISCUSSION

Two of the three participants improved from baseline on the BNT short form, responsive naming, and category naming. One of these participants also improved on sentence repetition (003), while the other (001) improved on auditory word discrimination and auditory commands. In six of the eight subtests for which statistical change occurred, improvement persisted beyond the immediate assessment to one or both of the 1 and 4 week follow-ups. Together

Table 2 | BDAE scores for participant 001.

		Pre1	Pre2	Post1	Post2	Post3
Naming	BNT (15)	2	2	6*	7*	5*
	Colors (4)	0	0	0	0	0
	Animals (12)	3	3	2	4	4
	Actions (12)	2	4	6	4	4
	Tools (12)	2	2	5*	6*	3
	Responsive naming (20)	1	3	7*	4	2
Connected speech	Cookie theft	3	1	1	1	1
Repetition	Single words (10)	7	7	8	8	7
	Non-sense words (5)	2	3	3	4	2
	Sentences (10)	0	1	0	0	0
Auditory C'hension	Word discrimination (37	21	24	30*	30*	26
	Commands (15)	6	6	10*	9*	10*
	Complex Ideational (12)	2	2	2	1	0

**Denotes score greater than two standard errors from the baseline mean. Parenthesized values denote maximum score for that subtest. Pre1 and Pre2 = first and second baseline assessment sessions, respectively. Post1, 2, and 3 = assessment sessions conducted immediately, 1 and 4 weeks after CVS, respectively.*

these data give the first tentative support for the idea that CVS can relieve both expressive and receptive elements of aphasia.

We note that recovery patterns diverged across subtests and patients. On the category naming tests, 001 improved on tools while 003 improved on actions and animals. Only 001 improved on the auditory word discrimination and commands while 002 showed no improvement on any test. It is difficult to determine the source of this variation, although category naming is known to vary considerably across aphasics (Goodglass et al., 1966; see also Hillis and Caramazza, 1991), while the failure of 003 to match 001's improvement on the comprehension tasks partly reflects the fact that his scores were already at or near ceiling during baseline assessment. The failure of 002 to respond is more troubling, though his radiology shows greater temporal-parietal-frontal encroachment than the others, and he also suffered from severe apraxia of speech which resulted in much lower baseline scores.

Perhaps of more concern is the potential impact of natural recovery and placebo. We are reluctant to attribute high importance to natural recovery because all patients were in the sub-acute/chronic phase (i.e., were at least 8 months post-onset). During this time, it would be surprising if substantial changes in language and communication occurred over the course of a 5-week study period. That said, Participant 003 had already showed modest change in the few months leading up to study, but the degree of change shown after enrolment surprised his physicians

Table 3 | BDAE scores for participant 002.

		Pre1	Pre2	Post1	Post2	Post3
Naming	BNT (15)	0	0	0	0	0
	Colors (4)	0	0	0	0	0
	Animals (12)	1	0	1	1	0
	Actions (12)	1	1	2	2	0
	Tools (12)	0	0	0	0	0
	Responsive naming (20)	0	0	0	0	0
Connected speech	Cookie theft	4	1	0	1	2
Repetition	Single words (10)	1	1	2	0	0
	Non-sense words (5)	0	0	0	0	0
	Sentences (10)	0	1	0	0	0
Auditory C'hension	Word discrimination (37)	32	29	31	31	32
	Commands (15)	12	14	14	14	13
	Complex Ideational (12)	6	4	6	6	7

Table 4 | BDAE scores for Participant 003.

		Pre1	Pre2	Post1	Post2	Post3
Naming	BNT (15)	5	6	8*	4	8*
	Colors (4)	2	3	2	3	3
	Animals (12)	4	5	8*	6	6
	Actions (12)	5	5	7*	7*	6
	Tools (12)	3	5	5	7	5
	Responsive naming (20)	3	6	11*	10*	9
Connected speech	Cookie theft	1	6	4	4	4
Repetition	Single words (10)	6	8	9	8	9
	Non-sense words (5)	3	4	4	4	4
	Sentences (10)	3	4	7*	6*	6*
Auditory C'hension	Word discrimination (37)	37	37	36	36	37
	Commands (15)	14	14	15	15	14
	Complex Ideational (12)	8	8	9	8	6

**Denotes score greater than two standard errors from the baseline mean.*

and carers. It also seems unlikely that any natural recovery would coincide most strongly with the immediate and week 1 follow-ups rather than the later week 4 follow-up. Such a pattern would be more consistent with a placebo effect. However, if the treatment exerted a strong placebo effect then why did only some of the outcome scores change? And why would both participants show change on the BNT and responsive naming tasks, as opposed to more idiosyncratic and divergent patterns? We can find no evidence from elsewhere that these tasks are more susceptible to placebo effects than other BDAE subtests. More generally, sham-controlled studies involving other forms of non-invasive neuro-stimulation report that the placebo effect in aphasic participants tends to be low. For example, Monti et al. (2008) reported that, relative to baseline, cathodal tDCS improved picture naming by 34% while sham led to a 0.4% improvement. Similarly, Barwood et al. (2012) reported that while active rTMS induced an improvement in overall BDAE score of 18.5 points, sham rTMS induced a change of just 0.17.

How might CVS have contributed to the observed recovery? As mentioned above, right-sided stimulation has been shown to increase metabolic activity in left hemisphere language networks (Baker et al., 2010; Hamilton et al., 2010; Fiori et al., 2011; Szaflarski et al., 2011) and also modulates the distal release of acetylcholine and monoamines relevant to language recovery (Horii et al., 1994; Nishiike et al., 2001; Klein and Albert, 2004; Ma et al., 2007). Of particular interest, increased release of noradrenaline and acetylcholine is associated with naming improvement and verbal memory in aphasic patients (Tanaka et al., 1997; Beversdorf et al., 2007), while increased serotonin can exert a positive effect on language recovery, most likely by counteracting depression and anxiety (Laino, 2004). These projection systems are usually characterized as diffuse rather than unilateral which raises the question of whether they are influenced by the side of caloric stimulation? Unfortunately, microdialysis neurotransmitter studies have yet to compare left versus right CVS so the extent to which the recovery seen here arises from non-lateralised mechanisms remains unclear.

On a related note, given that CVS is associated with recovery from a range of other neuropsychological and psychiatric impairments, we are reluctant to attribute the recovery seen in our participants to a language-specific mechanism. More likely is something akin to the domain-general mechanism described by Schiff and Pulver (1999) in which CVS helps engage a thalamic cortico–cortico gating mechanism involved in the reactivation and reintegration of injured cortical areas and/or the recruitment of novel areas. In addition to this, increases in arousal and alertness may enhance susceptibility to placebo effects within the clinical setting.

On a final, more anecdotal point, the testimonials reported above allude to co-morbid improvements in motor function (see Testimonials 2 and 3). Participant 001, who was previously only able to transfer and walk short distances with assistance, was now able to mobilise independently between rooms in the house with the aid of a walking stick. She was able to transfer herself more independently, reporting that this was due to increased control of her right lower limb. Similarly, participant 002 reported an increased control and flexibility in his right lower limb, resulting in more independent movement around the house. 002 still required supervision when climbing the stairs, however he reported that where before this would take up to 10 min, he was now able to complete the task in approximately 5 min. These observations chime with the findings of Sturt and Punt (2013) who recently showed improved postural control in a group of hemi-spatial neglect patients post-CVS, and give reason to assess motor outcome in future studies.

In summary, we provide preliminary evidence that CVS may help relieve both expressive and receptive symptoms of aphasia. A larger-scale, dose-response, sham-controlled study that specifies a broader range of endpoints involving reading, writing, and activities of daily living, would now seem sensible. Coupled with

the beneficial effects of CVS on other stroke conditions such as hemi-spatial neglect (Cappa et al., 1987), pain (McGeoch et al., 2008), and hemi-anesthesia (Bottini et al., 2005), the current data also strengthen the growing idea that CVS triggers a generic compensatory response to brain trauma which may be of relevance to a wide variety of neurological conditions. Given the need for many different brain systems to know if the head is upright, moving and if so, in what direction and at what speed, we believe that the therapeutic reach of vestibular stimulation will prove considerable.

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Galvanic vestibular stimulation in hemi-spatial neglect

David Wilkinson[1]*, Olga Zubko[1], Mohamed Sakel[2], Simon Coulton[3], Tracy Higgins[3] and Patrick Pullicino[2]

[1] School of Psychology, University of Kent, Canterbury, UK
[2] East Kent Neuro-Rehabilitation Service, East Kent Hospitals University NHS Foundation Trust, Canterbury, UK
[3] Centre for Health Services Studies, University of Kent, Canterbury, UK

Edited by:
Christophe Lopez, Centre National de La Recherche Scientifique, France

Reviewed by:
Arnaud Saj, University Hospital of Geneva, Switzerland
Kathrin S. Utz, Friedrich-Alexander University Erlangen-Nuremberg, Germany

***Correspondence:**
David Wilkinson, School of Psychology, University of Kent, Canterbury, Kent CT2 7NP, UK
e-mail: dtw@kent.ac.uk

Hemi-spatial neglect is an attentional disorder in which the sufferer fails to acknowledge or respond to stimuli appearing in contralesional space. In recent years, it has become clear that a measurable reduction in contralesional neglect can occur during galvanic vestibular stimulation, a technique by which transmastoid, small amplitude current induces lateral, attentional shifts via asymmetric modulation of the left and right vestibular nerves. However, it remains unclear whether this reduction persists after stimulation is stopped. To estimate longevity of effect, we therefore conducted a double-blind, randomized, dose-response trial involving a group of stroke patients suffering from left-sided neglect ($n = 52$, mean age = 66 years). To determine whether repeated sessions of galvanic vestibular stimulation more effectively induce lasting relief than a single session, participants received 1, 5, or 10 sessions, each lasting 25 min, of sub-sensory, left-anodal right-cathodal noisy direct current (mean amplitude = 1 mA). Ninety five percent confidence intervals indicated that all three treatment arms showed a statistically significant improvement between the pre-stimulation baseline and the final day of stimulation on the primary outcome measure, the conventional tests of the Behavioral Inattention Test. More remarkably, this change (mean change = 28%, $SD = 18$) was still evident 1 month later. Secondary analyses indicated an allied increase of 20% in median Barthel Index (BI) score, a measure of functional capacity, in the absence of any adverse events or instances of participant non-compliance. Together these data suggest that galvanic vestibular stimulation, a simple, cheap technique suitable for home-based administration, may produce lasting reductions in neglect that are clinically important. Further protocol optimization is now needed ahead of a larger effectiveness study.

Keywords: stroke, neuro-stimulation, clinical trial, hemi-inattention, rehabilitation

INTRODUCTION

Hemi-spatial neglect is a debilitating, attentional disorder that most commonly arises from damage to the right-side of the brain (Robertson and Halligan, 1999). Sufferers fail to acknowledge or respond to visual information presented on the side of space opposite their brain lesion (e.g., the left), and as such struggle with many daily routines, characteristically bumping into obstacles, failing to notice people on the affected side or cleaning only one side of their body. Prevalence is hard to estimate because diagnostic criteria differ, but conservative estimates indicate that of the ∼150,000 UK residents who suffer a stroke per year, approximately 18% (i.e., 27,000) will show moderate to severe left-sided neglect in the acute phase, with ∼7% (i.e., 10,000) continuing to show stable impairment beyond 3 months (Ringman et al., 2004). Unfortunately, the presence of left neglect is very strongly associated with poor general functional outcome. Individuals with neglect (regardless of severity) typically require additional weeks in hospital (Katz et al., 1999; Wilkinson et al., 2012), need nearly twice as many hours of physiotherapy and occupational therapy, and are more prone to falls and persistent urinary incontinence (Paolucci et al., 2001). Compared to others with the same Barthel Index (BI) score at hospital admission, patients with neglect score significantly lower on measures of functional independence both during hospital stay and 18 months after leaving (Jehkonen et al., 2000; Gillen et al., 2005; Nijboer et al., 2013). Those who still show neglect on simple bedside tests 2 months after admission have a higher risk of functional worsening at 1 year follow-up. Post discharge, patients with neglect are more likely to require ambulatory assistance and long-term institutionalization or assisted living Kalra et al., 1997; Katz et al., 1999; Nijboer et al., 2013.

Regrettably, many cases of neglect are refractory to treatment. According to a Cochrane Review conducted in 2013, "the effectiveness of rehabilitation strategies for reducing the disabling effects of neglect and increasing independence remains unproven," (Bowen et al., 2013, p. 1). The review pointed out that although several new treatment approaches meet proof-of-concept, too few studies have progressed these to the level of randomized, controlled trials.

Near complete, but transient, relief from neglect has been observed during artificial stimulation of the vestibular nerves (Rubens, 1985; Cappa et al., 1987). These nerves send information from the semi-circular canals and otoliths of the inner ear to, among other brain regions, parts of the peri-sylvia involved in spatial attention and awareness (Suzuki et al., 2001; Balaban

et al., 2011). The conventional method, caloric vestibular stimulation, involves the injection of thermal current (usually via cold water) into the ear canal. This alters the density of endolymph within the nearby balance organs and in turn modulates their afferent firing patterns (see Miller and Ngo, 2007). Unfortunately, the therapeutic benefit of CVS is offset by severe vertigo, nausea and the more general impracticality of ear irrigation, all of which hinder repeated use.

Recent studies suggest that a related technique, known as galvanic vestibular stimulation may provide a more tolerable and simpler way of harnessing this beneficial effect (see Utz et al., 2010). GVS involves the delivery of tiny electrical currents via two small electrodes to the mastoid processes which overlie the vestibular nerves (Coats, 1972). The currents modulate the firing rates of the vestibular nerves in a similar manner to natural head movement, inducing broad-scale compensatory responses across cortical and subcortical regions (Bense et al., 2001; Wilkinson et al., 2012). The electric currents are applied at a level (∼1 mA) that is too low to be felt by the patient and without the need for patient agency or motivation which are often compromised in neglect.

Preliminary studies show that a single 15–30 min session of GVS improves performance across a range of visuo-spatial tasks including line bisection, figure copying and target cancellation (Rorsman et al., 1999; Wilkinson et al., 2010; Utz et al., 2011a). Several recent studies also hint, but by no means confirm, that the beneficial effects of GVS persist after stimulation is stopped. In an unblinded study performed on two neglect patients, Zubko et al. (2013) showed that a week's programme of GVS was associated with statistically fewer omissions on the star and letter cancellation tasks 3 days post-stimulation. In two other small-group studies conducted on non-neglectors, Kerkhoff and colleagues showed that GVS induced lasting relief for up to 12 weeks from the somatosensory disorder of tactile extinction (Kerkhoff et al., 2011; Schmidt et al., 2013). Given that these studies provide only indirect support for the idea that GVS can induce lasting carry-over from neglect, the need arises for a more reliable estimate of the duration and magnitude of recovery. If, under more tightly controlled and adequately powered conditions, proof of carry-over can be shown then further investigations into the rehabilitative potential of GVS would be warranted.

Most forms of neuro-rehabilitation tend to rely on repeated application to induce carry-over, a finding that chimes with the recent discovery that experience-dependent, long-term plastic change requires multiple stimulus exposures (Hoffman and Cavus, 2002). In the case of hemi-spatial neglect, several techniques other than GVS (e.g., transcranial magnetic stimulation, optokinetic stimulation) have induced gains, albeit of limited scope, for 2 weeks or more following 5–10 consecutive, 30 min daily sessions (Kleinjung et al., 2005; Shindo et al., 2006; Naeser et al., 2012). Similar treatment periods have induced long-term remission from other neuropsychological disorders (McKay et al., 2002; Ohn et al., 2008). These studies suggest that repeated administration not only increases the length of recovery, but also the magnitude of recovery. Contrary to the preliminary data described above (Kerkhoff et al., 2011; Schmidt et al., 2013; Zubko et al., 2013), these studies imply that GVS may be most effective when repeatedly, as opposed to singularly, applied.

The present study had two specific aims: to establish whether (1) GVS can induce a recovery from neglect that lasts beyond the stimulation period, and (2) carry-over is more effectively induced via a single or repeated sessions. To test these hypotheses we allocated, at random, 52 experimental volunteers with left-sided hemi-spatial neglect to one of three treatment arms in which they received 1, 5, or 10 sessions of subliminal GVS, with those in the 1 and 5 treatment arms also receiving 9 and 5 sham sessions respectively. Follow-up tests and questionnaires were conducted 1, 2, and 4 weeks later to assess the severity of neglect symptoms, transfer to activities of daily living, and compliance.

MATERIALS AND METHODS

PARTICIPANTS

Participants were recruited between July 2011 and November 2012 from nearby acute stroke and neuro-rehabilitation units in South East England, although a handful of participants self-referred from other parts of the UK following national media coverage. Individuals were eligible if they scored ≤129 on the conventional tests of the Behavioral Inattention Test (BIT) (Halligan et al., 1987); suffered a right unilateral stroke (confirmed by CT or MRI scan); ≥6 weeks post-stroke; ≥18 years; scored ≤2 on the 6-item screener for dementia (Callahan et al., 2002), and scored ≤29 on the Beck Depression Inventory (Beck et al., 1996). Individuals with neglect and suspected visual field loss were included because there is evidence that they can still benefit from GVS (e.g., Rorsman et al., 1999; Wilkinson et al., 2005; Utz et al., 2011a). The presence of hemianopia was not recorded for study purposes because formal field perimetry was not available for many participants. Individuals with titanium plates were also included provided these did not lie beneath or directly adjacent to the stimulation sites. Individuals were excluded if they showed evidence of moderate to severe aphasia on clinical examination and/or prior significant neurological or vestibular illness. Patients with electronic implants, such as cardiac pacemakers, were also excluded given the potential for electrical interference from the vestibular stimulator.

RECRUITMENT, ALLOCATION, AND BLINDING

All participants were informed of the study and provided written informed consent prior to assessment. The study received NHS ethical approval from the London City & East NRES committee, and was conducted in accordance with Medical Research Council (UK) Good Clinical Practice guidelines and the Declaration of Helsinki. Prior to participant enrolment, the trial was registered on the UK Clinical Research Network Study Portfolio Database (UKCRN ID: 10505).

Patients who met eligibility were randomly assigned to one of the three treatment arms (1 active and 9 sham treatments vs. 5 active and 5 sham treatments vs. 10 active and 0 sham treatments) using minimization controlling for age (60 years or more vs. less than 60 years), inpatient/outpatient status, and severity of neglect as measured by the conventional measures of the BIT. Randomization was conducted using a secure, remote randomization facility independent of the research team.

Treatment allocation was double-blind; since the GVS was sub-sensory participants did not know their allocation, and a stimulation protocol (active or sham) pre-determined by the randomization officer was naively administered by the experimenter by typing a 4 digit code (which changed every time) into the stimulation device. Participants' in-patient neglect treatment (typically visual scanning therapy but sometimes limited to the informal reminders given by occupational therapy staff to look left during functional activities) was suspended while they remained on-study. Treatment begun within 1 week of baseline assessment.

OUTCOME MEASURES

The primary outcome measure, severity of neglect 4 weeks post-stimulation, was measured using the conventional measures of the BIT. Transfer to activities of daily living was measured using the BI (Mahoney and Barthel, 1965). The BIT and BI were administered by the experimenter at baseline, on the final day of stimulation, and then 1, 2, and 4 weeks post-stimulation. Participant well-being was captured via daily diary cards and an end-of-study satisfaction questionnaire which were completed by the participant often with the help of a relative or friend.

TREATMENT PREPARATION

Bipolar, binaural current was delivered through a pair of 2 × 4 cm carbon-rubber, self-adhesive, disposable stimulating electrodes placed over participants' mastoid processes. To ensure complete electrical contact with the electrodes, surrounding skin was cleansed with an alcohol swab and conductive gel coated on the undersides of the electrodes. To induce leftward deviation in the lateral plane, the anode was placed over the left mastoid and the cathode over the right mastoid. The electrodes were connected to a *Magstim Eldith Transcranial DC Stimulator Plus*™ device that was pre-programmed to deliver either 0 or 1 mA mean (0.5–1.5 mA) noisy current for 25 min. Earlier pilot work indicated that older, stroke patients rarely report the presence of a noisy 1 mA DC waveform. In line with this, the incidence with which our participants reported unusual sensations during stimulation, such as

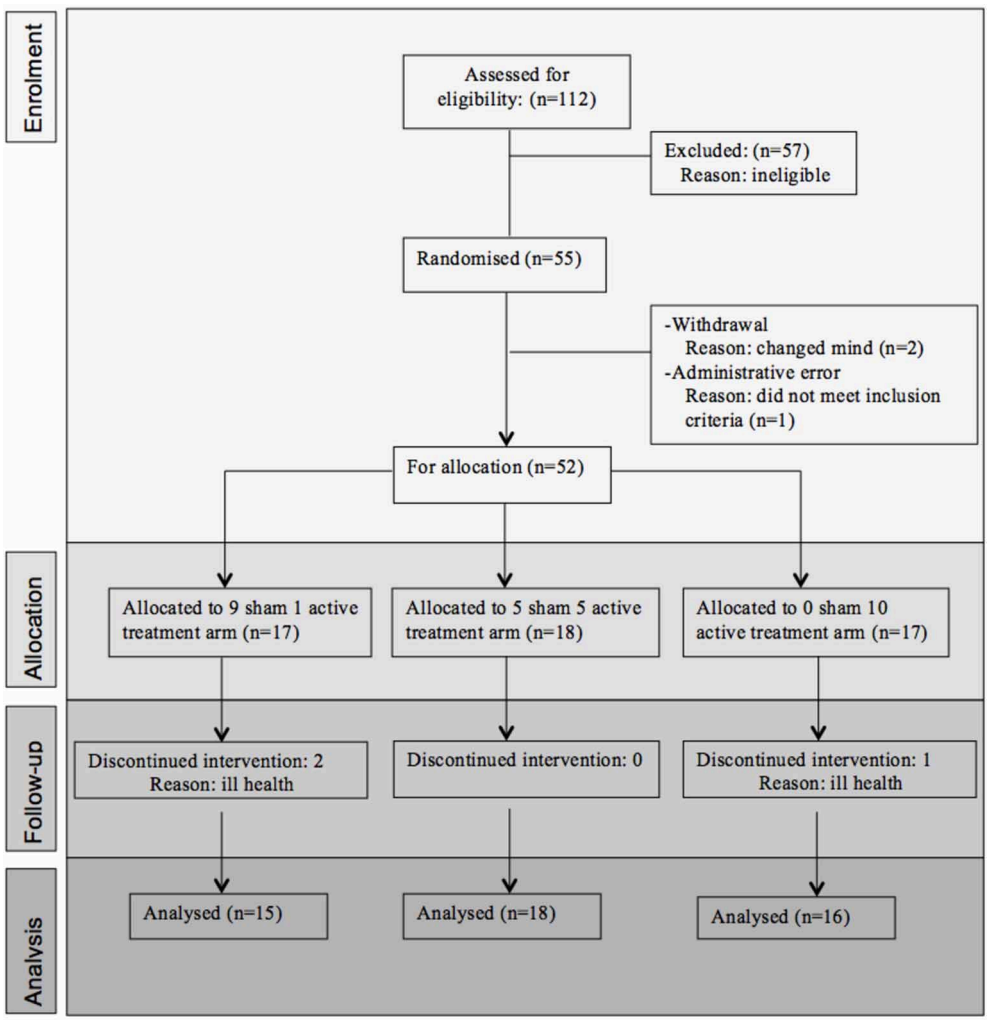


FIGURE 1 | Consort statement.

pain, tingling or itching behind the ears, were no greater than at the "no stimulation" baseline (see **Table 12**). Participants were informed that although all participants would receive at least one session of active stimulation, the number of active sessions would vary from participant to participant. During stimulation, participants rested and remained either seated or positioned upright in bed. Stimulation was performed daily from Monday to Friday for two consecutive weeks. All sham sessions were administered first to ensure that, across participants, equal time had elapsed between the final session of active stimulation and the first follow-up assessment. This meant that in the 1 active condition, active stimulation was administered on the final (i.e., 10th) stimulation day, while participants in the 5 active condition received active stimulation from days 6 to 10.

RESULTS

Fifty-five participants were considered eligible, provided consent and randomized (see **Figure 1**). Of these, 6 participants did not complete the treatment protocol resulting in a total of 49 patients with evaluable data across the three treatment regimens. This number allowed us to meet our target enrolment of 15 participants per treatment arm which was deemed sufficient to allow a potential effect size difference of 0.8 to be detected at 80% power and an alpha of 0.05. The sample demographic characteristics were similar across all three arms (see **Table 1**).

The analysis was conducted as a per protocol analysis, in that only those who completed the intervention and follow-up were evaluated. The primary outcome measure, BIT score at 4 weeks stimulation, was evaluated using an analysis of covariance adjusting for the baseline covariates of BIT score at enrolment, in/out patient status, and age. Analyses of the BI scores were also adjusted for these covariates. Summary data were collated for descriptive analyses of the sub-tests/sub-scales of the BIT and BI, and to show the level of participant satisfaction and the incidence/nature of adverse events. Given the unexpected variation in time since stroke across treatment arm (see **Table 1**), exploratory analyses were also conducted *post hoc* using the analysis of covariance described above but with Time since Stroke as an additional co-variate to explore its impact on the primary and secondary outcome measures.

Table 1 | Summary of demographic data.

		Treatment regimen		
		1 Active	**5 Active**	**10 Active**
Total *N*		15	18	16
Age (years)	Mean	66.9	66.0	65.7
	SD	10.6	9.37	8.72
	Median	66.0	66.5	66.0
	Range	33	38	33
Gender (*N*)	Male	12	12	13
	Female	3	6	3
Ethnicity (*N*)	White European	15	18	16
Patient type (*N*)	Inpatient	10	9	9
	Outpatient	5	9	7
Time since stroke (days)	Median	68	75	94
	Interquartile range	39–229	41–479	39–534

BEHAVIORAL INATTENTION TEST

Table 2 presents measures of central tendency and dispersion for each treatment arm. **Table 3** shows the *p*-values from the

Table 2 | Summary of BIT scores.

		Treatment regimen		
		1 Active	**5 Active**	**10 Active**
Baseline	Mean	73.3	78.7	85.0
	SD	40.2	34.0	35.9
	Median	81	83	97
	Minimum	13	15	28
	Maximum	124	125	124
	Range	111	110	96
	N	15	18	16
Session 10	Mean	92.9	96.3	97.4
	SD	38.9	36.0	38.1
	Median	97	110	113
	Minimum	21	37	17
	Maximum	143	142	140
	Range	122	105	123
	N	15	18	16
Week 1	Mean	94.9	104	96.9
	SD	37.3	31.7	38.7
	Median	108	122	106.5
	Minimum	15	53	21
	Maximum	143	143	139
	Range	128	90	118
	N	15	15	16
Week 2	Mean	101	102	97.1
	SD	36.7	34.1	36.0
	Median	111	119	106
	Minimum	19	53	31
	Maximum	145	146	138
	Range	126	93	107
	N	15	17	16
Week 4	Mean	99.6	99.9	104
	SD	39.8	35.8	39.3
	Median	111	113	122
	Minimum	19	28	26
	Maximum	146	144	142
	Range	127	116	116
	N	15	18	16
AUC (0–4 weeks)	Mean	393	424	395
	SD	150	127	147
	Median	430	489	460
	Minimum	73	229	102
	Maximum	578	577	545
	Range	505	348	443
	N	15	15	16

AUC, area under the curve.

corresponding ANCOVA of the adjusted mean scores, and highlights a significant association between mean BIT score at baseline and all subsequent sessions. Adjusted mean BIT scores (change from baseline) and corresponding 95% confidence intervals are shown in **Figure 2**, and indicate that the change in BIT score between baseline and 4 weeks post-GVS was statistically significant in all treatment arms. These changes were associated with large effect sizes: Cohen's *d* for 1 active, 5 active, and 10 active arms = 0.97, 1.29, and 1.48, respectively. The pattern of non-overlapping/overlapping confidence intervals in **Figure 2** also indicate that the BIT scores at all other time-points were statistically different from baseline, although there were no statistically significant differences between treatment arms (see **Table 4**). The improvement in overall BIT performance from baseline to week 4 was evident on all sub-tests in all treatment arms, except for figure/shape copying in the 1 active arm, and free drawing in the 5 and 10 active arms (see **Table 5**). The differences across treatment arms in BIT sub-test scores at baseline and week 4 are depicted in **Table 6**, and although some appear to be marked, the statistical analysis did not show statistically significant differences. Likewise, the exploratory analysis indicated that Time since Stroke did not significantly affect outcome (see **Tables 7**, **8**).

Table 3 | Results from statistical analysis of BIT.

	Analysis of covariance (*p*-values)				
	Treatment	**Treatment (linear)**	**Baseline**	**Age**	**Patient status**
Week 4	0.678	0.383	<0.001	0.0784	0.0670
AUC (0–4 weeks)	0.254	0.0964	<0.001	0.0943	0.360
Session 10	0.566	0.297	<0.001	0.0533	0.645
Week 1	0.432	0.200	<0.001	0.39	0.584
Week 2	0.0865	0.0261	<0.001	0.0203	0.330

BARTHEL INDEX

Table 9 presents measures of central tendency and dispersion for each treatment arm. **Table 10** shows the *p*-values for the corresponding ANCOVA and highlights a significant association between baseline BI score and the subsequent sessions. All adjusted BI median scores (change from baseline) and corresponding 95% confidence intervals are shown in **Figure 3**, and indicate that the change in BI median score between baseline and 4 weeks post-GVS was statistically significant in the 1 active treatment arm (though analysis of the ranked data showed that this change was also statistically significant in both other treatment arms). The pattern of overlapping confidence intervals indicates that there were no reliable differences between treatment arms. Summary data for the 1 active condition indicated that improvement was most evident on the bathing, bladder, bowels, and transfer (from bed to chair) sub-scales (see **Figure 4**). As with the BIT data, the exploratory analysis indicated that Time since Stroke did not significantly affect outcome (see **Table 11**).

ADVERSE EVENTS AND PARTICIPANT SATISFACTION

Table 12 presents summary data collected from participants' diary cards before and during the stimulation period. Relative to baseline, there was little evidence in any treatment group of increased sickness, headache, tiredness, dizziness, pain behind ears or visual disturbance. Participants in all treatment arms reported favorable opinions on the satisfaction questionnaire (see **Table 13**).

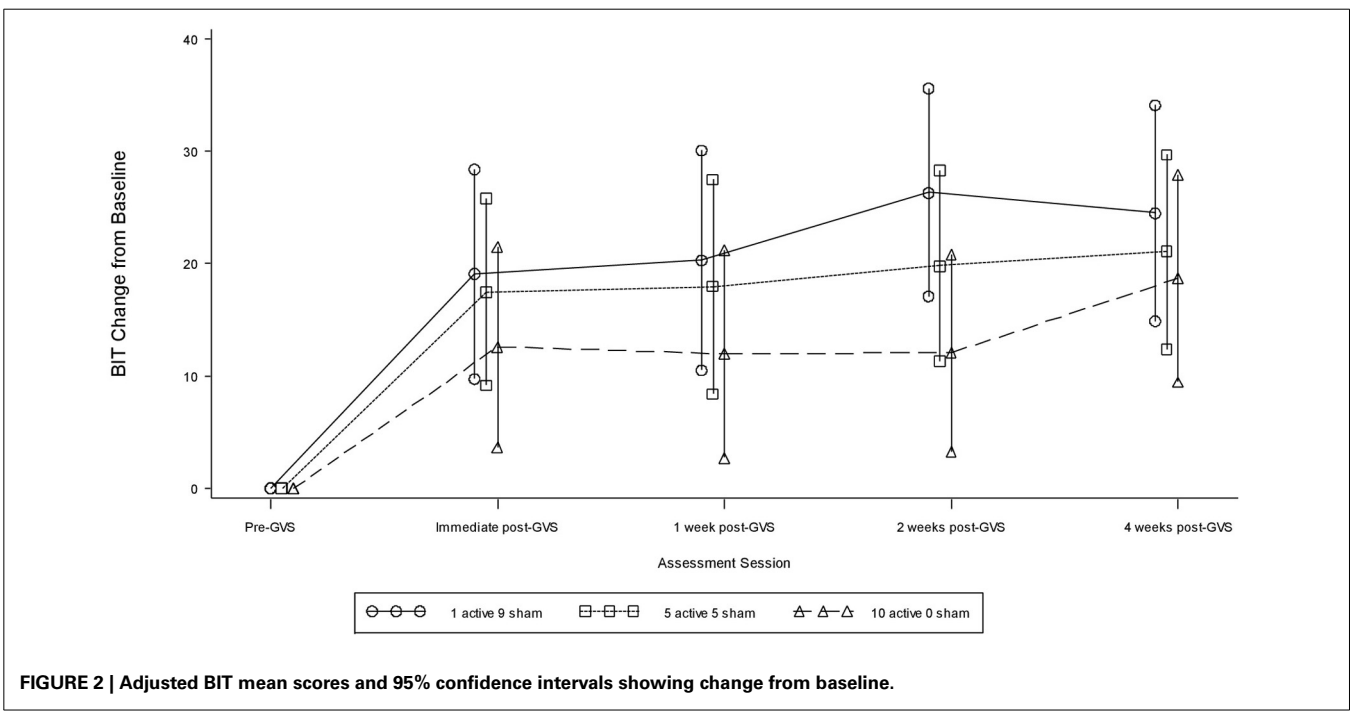


FIGURE 2 | Adjusted BIT mean scores and 95% confidence intervals showing change from baseline.

Table 4 | BIT adjusted means and 95% confidence intervals—treatment differences.

	Adjusted means (95% confidence intervals) Treatment difference		
	5 Active – 1 Active	**10 Active – 1 Active**	**10 Active – 5 Active**
Week 4	−3.44 (−16.4 to 9.49)	−5.83 (−19.1 to 7.48)	−2.38 (−15.0 to 10.2)
AUC (0–4 weeks)	−15.0 (−64 to 33.9)	−39.1 (−86.7 to 8.53)	−24.1 (−71.2 to 23.1)
Session 10	−1.57 (−14.1 to 10.9)	−6.48 (−19.3 to 6.38)	−4.92 (−17.1 to 7.28)
Week 1	−2.35 (−16.2 to 11.5)	−8.35 (−21.8 to 5.09)	−5.99 (−19.3 to 7.30)
Week 2	−6.54 (−19.1 to 6.06)	−14.3 (−27.0 to −1.59)	−7.76 (−20.0 to 4.44)

Table 5 | Median scores on BIT sub-tests as function of number of active sessions.

No. active	**BIT sub-tests**																	
	Star cancellation (max = 54)			**Letter cancellation (max = 40)**			**Line bisection (max = 9)**			**Line crossing (max = 36)**			**Copying (max = 4)**			**Free drawing (max = 4)**		
	1	5	10	1	5	10	1	5	10	1	5	10	1	5	10	1	5	10
Baseline	24	29	35	19	24	26	3	3	2	29	24	35	1	1	1	0	2	2
Session10	31	39	42	25	31	32	4	3	4	35	35	36	2	1	2	2	2	2
Week 1	42	36	39	24	30	26	4	4	4	33	35	35	1	2	2	2	2	3
Week 2	45	45	38	28	28	30	4	4	3	36	36	36	1	2	2	2	2	2
Week 4	47	38	42	25	33	33	4	6	5	35	34	36	1	2	2	2	2	2
Week 4-baseline	23	9	7	6	9	7	1	3	3	6	10	1	0	1	1	2	0	0

Parenthesized values denote maximum possible score. The bottom row shows change from baseline to week 4.

Table 6 | Inter-arm differences in median scores on BIT sub-tests at baseline and week 4.

No. active	**BIT sub-tests**																	
	Star cancellation			**Letter cancellation**			**Line bisection**			**Line crossing**			**Copying**			**Free drawing**		
	1–5	**1–10**	**5–10**	**1–5**	**1–10**	**5–10**	**1–5**	**1–10**	**5–10**	**1–5**	**1–10**	**5–10**	**1–5**	**1–10**	**5–10**	**1–5**	**1–10**	**5–10**
Baseline	−5	−11	−6	−5	−7	−2	0	1	1	5	−6	−11	0	0	0	−2	−2	0
Week 4	9	5	−4	−8	−8	0	−2	−1	1	1	−1	−2	−1	−1	0	0	0	0

To illustrate, for star cancellation the median score at baseline was 5 points lower in the 1 active arm compared to the 5 active arm. By week 4, the median score was 9 points higher in the 1 active arm compared to the 5 active arm.

Table 7 | Results from the exploratory statistical analysis of BIT including time since stroke as a co-variate.

	Analysis of covariance (*p*-values)					
	Treatment	**Treatment (linear)**	**Baseline**	**Age**	**Patient status**	**Time since stroke**
Week 4	0.733	0.542	<0.001	0.027	0.210	0.714
AUC (0–4 weeks)	0.352	0.196	<0.001	0.061	0.369	0.064

DISCUSSION

The marked improvement in mean BIT scores observed straight after the last stimulation session was still evident 4 weeks later. The scores recorded in this final follow-up were, for all treatment arms combined, 28% greater than those at baseline and gave rise to a large effect size (Cohen's $d > 1.0$). This improvement was observed within all treatment arms, was evident on all BIT sub-tests and was not affected by time since stroke. For participants in the single treatment arm, improvement transferred beyond the diagnostic measure of the BIT to the BI, a widely used, albeit relatively crude, measure of activities of daily living. Here there was a median improvement of 20%—a change considered to be clinically important, with changes most noticeable on the continence, bathing and transfer sub-scales. These changes were achieved in the absence of any reported adverse events and at a high level of participant compliance and satisfaction.

The comparable efficacy of a single versus multiple stimulation sessions is perhaps surprising given that most forms of cognitive rehabilitation rely on repeated administration. However, as mentioned in the Introduction, three, small GVS studies have shown

Table 8 | BIT adjusted means and 95% confidence intervals from the exploratory analysis including time since stroke as a co-variate—treatment differences.

	Adjusted means (95% Confidence intervals) Treatment difference		
	5 Active – 1 Active	**10 Active – 1 Active**	**10 Active – 5 Active**
Week 4	−4.95 (−18.7 to 8.85)	−4.46 (−18.6 to 9.69)	0.488 (−13.4 to 14.3)
AUC (0–4 weeks)	−29.7 (−82.1 to 22.6)	−33.3 (−83.2 to 16.5)	−3.59 (−54.9 to 47.1)

Table 9 | Summary of BI scores.

		Treatment regimen		
		1 Active	**5 Active**	**10 Active**
Baseline	Mean	42.9	53.8	71.3
	SD	27.4	32.8	26.8
	Median	40	50	80
	Minimum	0	5	20
	Maximum	90	100	100
	Range	90	95	80
	N	12	16	15
Session 10	Mean	49.6	60.8	62.3
	SD	24.1	29.1	31.0
	Median	50	70	65
	Minimum	5	20	15
	Maximum	75	100	100
	Range	70	80	85
	N	13	18	15
Week 1	Mean	59.1	65.3	61.1
	SD	27.3	27.4	21.9
	Median	70	70	55
	Minimum	0	20	25
	Maximum	85	100	100
	Range	85	80	75
	N	11	15	14
Week 2	Mean	57.5	53.2	63.3
	SD	30.9	27.4	25.9
	Median	60	45	65
	Minimum	5	15	25
	Maximum	95	95	100
	Range	90	80	75
	N	12	14	15
Week 4	Mean	64.3	56.9	66.4
	SD	24.5	25.6	26.5
	Median	67.5	57.5	70
	Minimum	0	15	25
	Maximum	90	100	100
	Range	90	85	75
	N	14	16	14

Table 10 | Results from statistical analysis of Barthel Index.

	Analysis of covariance (*p*-values)				
	Treatment	**Treatment (linear)**	**Baseline**	**Age**	**Patient status**
Week 4	0.361	0.172	<0.001	0.568	0.709
Session 10	0.494	0.581	<0.001	0.338	0.746
Week 1	0.566	0.405	<0.001	0.591	0.288
Week 2	0.894	0.650	<0.001	0.426	0.687

carry-over from a single session (Kerkhoff et al., 2011; Schmidt et al., 2013; Zubko et al., 2013). This may partly stem from the fact that the vestibular nerve is stimulated many thousands of times during a single 25–30 min session. This rate of stimulus repetition is much higher than that achieved with conventional behavioral interventions such as visual scanning therapy and contralesional limb activation and may, over a single session, be sufficient to induce long-term change in synaptic transmission (see Cooke and Bliss, 2006). The fact that these changes can be preferentially lateralized to the lesioned hemisphere via bipolar, binaural GVS may be particularly relevant given that neglect is associated with chronic under- and over-activation of the right and left hemisphere attentional systems respectively (Kinsbourne, 1977). The propensity for cortical change may be further enhanced by the distal up-regulation of key neurotransmitters within the brainstem during vestibular stimulation. Increased concentration of glutamate, a transmitter deemed especially important for NMDA-mediated synaptic excitability, has been observed within ascending pathways of the parabrachial nuclei and solitary tract during stimulation (Cai et al., 2007). Allied changes in serotonin release from the medial vestibular nuclei (Ma et al., 2007) and acetylcholine from hippocampal structures (Horii et al., 1994) may further facilitate recovery by heightening general arousal and alleviating co-morbid affective and cognitive disorders (Wilkinson et al., 2012).

On a cautionary note, the absence of a contemporaneous no-stimulation condition raises the question as to whether the improvement reported here was simply the result of natural recovery, practice and/or placebo. Such accounts cannot yet be ruled out with certainty. We chose not to include a no-stimulation condition because differences were expected between the treatment arms which would, given the blinding and minimization procedures employed, be sufficient to attribute at least some of the carry-over to GVS and thereby demonstrate proof-of-concept.

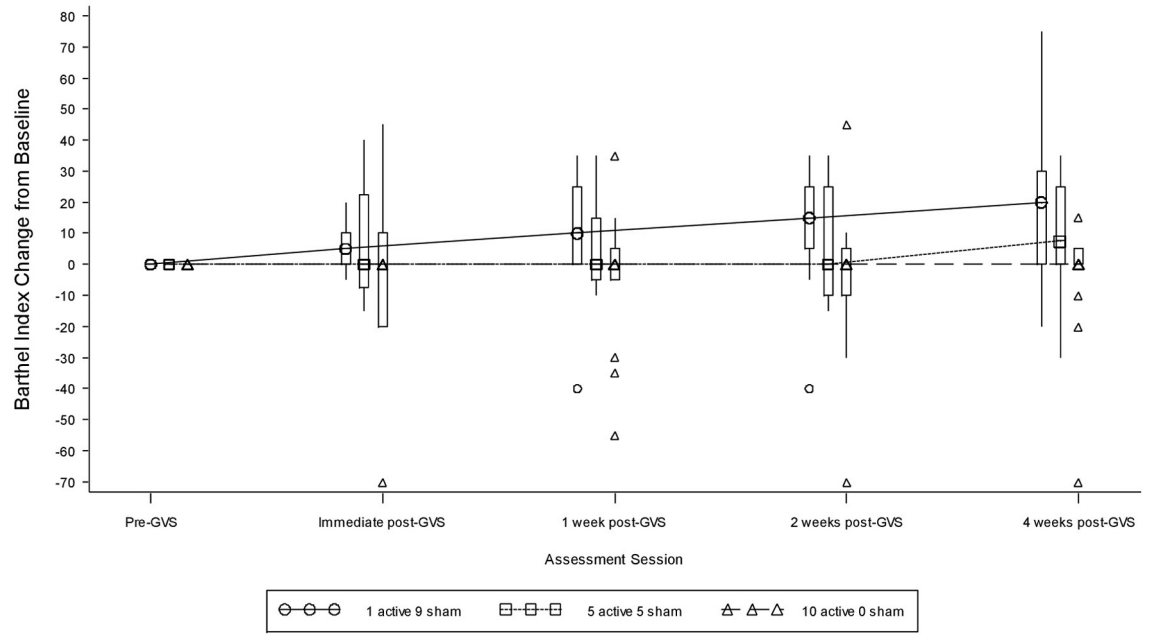


FIGURE 3 | Adjusted Barthel Index median scores showing change from baseline. The boxes represent the inter-quartile range and are intersected at their median point. The whiskers extend to the most extreme point within 1.5 times of the inter-quartile range.

Although treatment differences were not found, we believe it too coincidental for so many of the participants' natural recovery to be time-locked to the ∼2 week period between baseline assessment and the final day of stimulation, not least given their sub-acute and chronic status (recall that all patients were at least 6 weeks post-onset). If the initial improvement reflected increased familiarity with the test materials then, contrary to the results, one might have expected further improvement at the later sessions. Against a general practice effect, we also note that the test/retest reliability of the BIT across sessions spaced approximately 2 weeks apart (i.e., the time window in which most recovery occurred here) is high, yielding a correlation of 0.99 (Wilson et al., 1987). Regarding the potential influence of placebo, other neurostimulation studies have reported minimal placebo effects within this population (Nyffeler et al., 2009; Cazzoli et al., 2012; Koch et al., 2012). Aside from the use of blinding to counter placebo effects, the general absence of a strong placebo is also taken to reflect neglect patients' characteristic lack of affect and self-awareness. It also seems unlikely that any placebo occurring straight after stimulation would persist with the same intensity 1 month later, as observed here. Nevertheless, if this was the case then such a powerful placebo is, in its own right, worthy of further clinical investigation.

Aside from including a no-stimulation condition, we propose that further study should incorporate longer-term follow-up assessments. It remains possible that a greater number of sessions are more efficacious than a single one, but that longer follow-ups, perhaps in the order of months rather than weeks, are needed before this advantage becomes apparent. A second design issue concerns the best current amplitude to apply. We chose a 1 mA waveform because this is usually subliminal in older stroke patients yet known to modulate relevant neurophysiological and visual functions (Wilkinson et al., 2005, 2008, 2010, 2012; Zubko et al., 2013). But studies that perturb the vestibular stimulation via the more potent stimulus of ice-cold irrigation of the external ear canal have tended to eliminate (albeit transiently) rather than merely reduce neglect (Rubens, 1985; Cappa et al., 1987). The implication is that greater electrical currents may exert stronger relief than observed. The problem is that greater currents induce distracting side-effects, such as nausea and vertigo, and increase the risk of electrode burn. Future study therefore needs to establish if higher currents affect patient compliance within an acceptable margin. To this end, Utz et al. (2011b) recently demonstrated that, despite increased mild itching and tingling at the electrode sites, neglect patients were just as willing to receive GVS at 1.5 mA (super-sensory) as 0.6 mA. A key question is whether this willingness persists at even higher and potentially more efficacious levels. A final recommendation for future study is to incorporate multiple baseline assessments to better capture the rate of natural recovery. We excluded these assessments because the patients were sub-acute and the rate of natural recovery was assumed to be broadly comparable across treatment arm. But such repeat assessments must be included if studies are to now move beyond proof-of-concept and more accurately estimate treatment effect.

In closing, the current data endorse the growing sense that non-invasive neurostimulation may offer a viable alternative to pharmacological and behavioral interventions for neglect (Utz et al., 2010; Oliveri, 2011). Most neurostimulation research has focused on the potential benefits of transcranial direct current

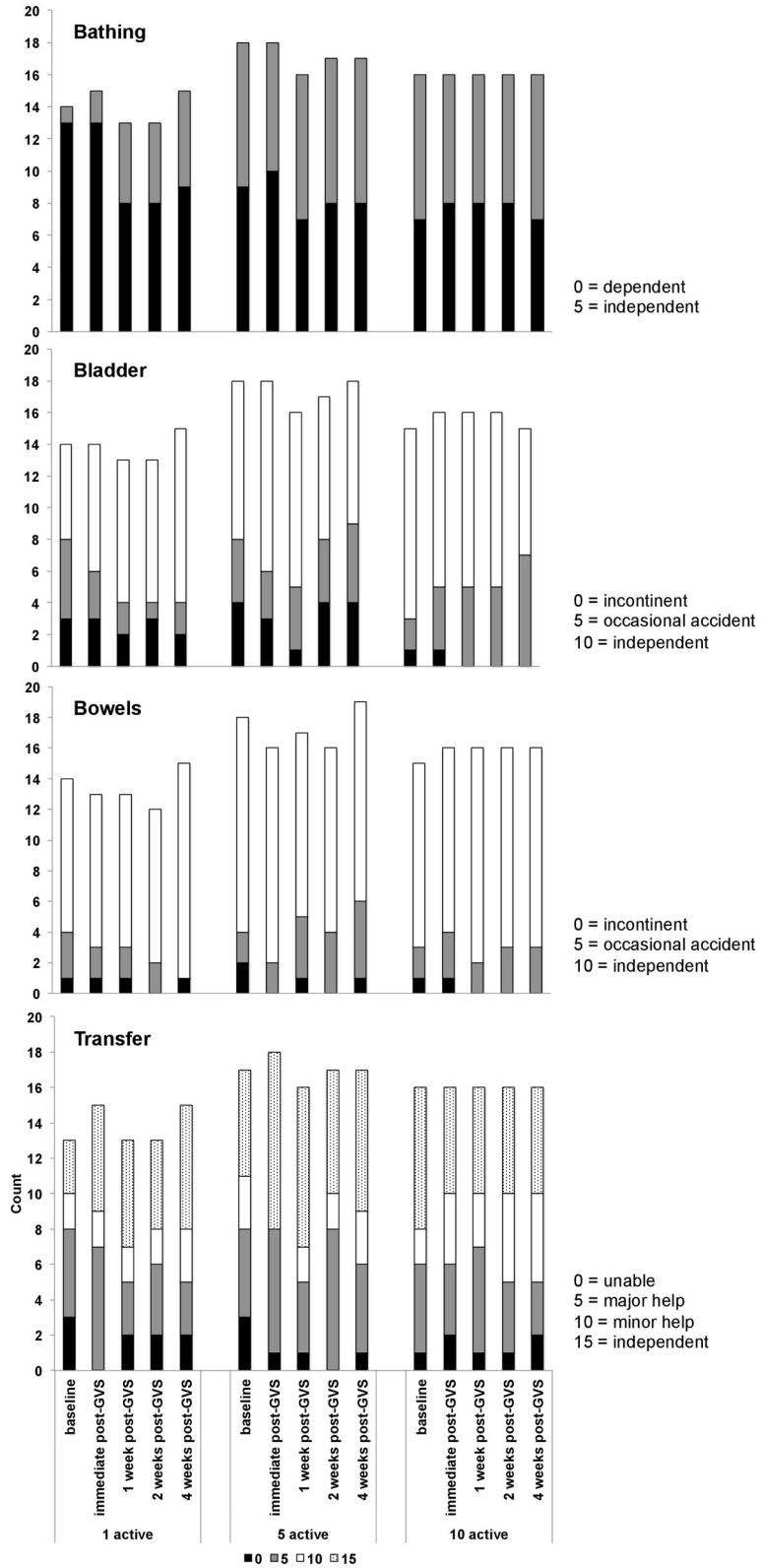


FIGURE 4 | Barthel index data showing the numbers of participants within each treatment arm who scored 0, 5, 10, or 15 on the bowels, bladder, bathing, and transfer sub-scales.

stimulation and transcranial magnetic stimulation. These techniques have also shown preliminary efficacy in neglect patients (see Müri et al., 2013). As in the present study, one recent TMS trial administered 10 daily sessions of stimulation and showed comparable improvement (23%) in BIT scores at 1 month follow-up (Koch et al., 2012). A subsequent study found that just 2 sessions of theta burst activity were sufficient to induce improvement for up to 3 weeks on the Catherine Bergego cale (Cazzoli et al., 2012), a measure of activities of daily living (Azouvi et al., 2003). However, the clinical application of these allied techniques still lacks systematic investigation—stimulation protocols need to be finessed, mechanistic bases elucidated, and too few studies incorporate adequate sample sizes, long follow-ups and measures of functional transfer (Müri et al., 2013; Yang et al., 2013). One advantage of GVS over these other stimulation methods is that delivery is simpler because there is no uncertainty about where on the scalp to apply stimulation—the electrodes are simply fastened to the mastoid processes. There is also no reported increase in seizure risk—if anything vestibular stimulation may reduce the likelihood of seizure onset (Kantner et al., 1982). In addition, GVS is cheap (relying on just a small battery, a simple micro-processor that can manage several stimulation parameters, two leads and a pair of electrodes), portable and suitable for home-based administration. Given the empirical data reported in the current study, we therefore recommend a further stage of optimization and efficacy testing before direct comparisons are made between GVS and these other emerging treatment options.

Table 11 | Results from exploratory statistical analysis of Barthel Index including time since stroke as a co-variate.

	Analysis of covariance (*p*-values)					
	Treatment	**Treatment (linear)**	**Baseline**	**Age**	**Patient status**	**Time since stroke**
Week 4	0.406	0.178	<0.001	0.630	0.679	0.934

Table 12 | Summary of participant diary data.

	1 Active			**5 Active**			**10 Active**		
	Baseline	**Days 1–5**	**Days 6–10**	**Baseline**	**Days 1–5**	**Days 6–10**	**Baseline**	**Days 1–5**	**Days 6–10**
SICKNESS									
Not at all	7	9	9	10	10	9	10	8	8
A little	2	0	0	1	0	1	0	1	1
Moderately	0	0	0	0	0	0	0	0	0
Very much	0	0	0	0	0	0	0	1	0
HEADACHE									
Not at all	6	7	9	5	7	8	9	7	6
A little	1	1	0	4	1	0	0	0	2
Moderately	0	1	0	2	1	0	1	3	0
Very much	0	0	0	0	1	2	0	0	1
TIREDNESS									
Not at all	1	1	1	6	6	5	1	0	0
A little	0	1	3	0	1	1	1	3	5
Moderately	4	5	4	3	1	2	5	3	2
Very much	3	2	1	2	2	2	3	4	2
DIZZINESS									
Not at all	8	9	9	11	10	9	10	9	7
A little	0	0	0	0	0	0	0	1	1
Moderately	0	0	0	0	0	1	0	0	1
Very much	0	0	0	0	0	0	0	0	0
PAIN BEHIND EARS									
Not at all	8	9	9	11	10	10	10	9	8
A little	0	0	0	0	0	0	0	1	0
Moderately	0	0	0	0	0	0	0	0	1
Very much	0	0	0	0	0	0	0	0	0
VISUAL DISTURBANCE									
Not at all	13	12	12	12	13	12	10	9	11
A little	1	2	1	0	0	0	2	4	2
Moderately	0	0	0	1	1	1	1	0	0
Very much	0	0	0	1	0	1	1	1	1

Table 13 | Participant satisfaction questionnaire.

Question	Response	Treatment regimen		
		9 Sham 1 Active	5 Sham 5 Active	10 Active
1. How has the course of treatment affected your awareness of your surroundings?	Much better	4	7	4
	A little better	6	7	7
	No different	3	3	3
	A little worse	0	0	0
	Much worse	0	0	0
2. In an overall, general sense how has the treatment made you feel about yourself?	Much better	3	5	2
	A little better	3	2	6
	No different	7	9	6
	A little worse	0	1	0
	Much worse	0	0	0
3. Was the treatment worth the effort of attending all the sessions?	Definitely yes	12	14	11
	Probably yes	1	3	2
	Not sure	0	0	1
	Probably no	0	0	0
	Definitely no		0	0
4. Are you happy with how the researchers behaved toward you?	Definitely yes	13	18	14
	Probably yes	0	0	0
	Not sure	0	0	0
	Probably no	0	0	0
	Definitely no	0	0	0
5. If a friend were in need of similar help, would you recommend our treatment to him or her?	Definitely yes	12	18	9
	Probably yes	1	0	4
	Not sure	0	0	1
	Probably no	0	0	0
	Definitely no	0	0	0

Values denote participant counts.

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The vestibular contribution to the head direction signal and navigation

Ryan M. Yoder [1] *† ***and Jeffrey S. Taube*** [2] *†

[1] Department of Psychology, Indiana University – Purdue University Fort Wayne, Fort Wayne, IN, USA
[2] Department of Psychological and Brain Sciences, Center for Cognitive Neuroscience, Dartmouth College, Hanover, NH, USA

Edited by:
Stephane Besnard, Institut National de la Santé et de la Recherche Médicale, France

Reviewed by:
John S. Butler, Trinity College Dublin, Ireland
Diego Manzoni, University of Pisa, Italy
Kishan Gupta, Boston University, USA

***Correspondence:**
Ryan M. Yoder, Department of Psychology, Indiana University – Purdue University Fort Wayne, Neff Hall 380C, 2101 East Coliseum Boulevard, Fort Wayne, IN 46805, USA
e-mail: yoderrm@ipfw.edu;
Jeffrey S. Taube, Department of Psychological and Brain Sciences, Center for Cognitive Neuroscience, Dartmouth College, 6207 Moore Hall, Maynard Street, Hanover, NH 03755, USA
e-mail: jeffrey.taube@dartmouth.edu

† *Ryan M. Yoder and Jeffrey S. Taube have contributed equally to this work.*

Spatial learning and navigation depend on neural representations of location and direction within the environment. These representations, encoded by place cells and head direction (HD) cells, respectively, are dominantly controlled by visual cues, but require input from the vestibular system. Vestibular signals play an important role in forming spatial representations in both visual and non-visual environments, but the details of this vestibular contribution are not fully understood. Here, we review the role of the vestibular system in generating various spatial signals in rodents, focusing primarily on HD cells. We also examine the vestibular system's role in navigation and the possible pathways by which vestibular information is conveyed to higher navigation centers.

Keywords: vestibular, semicircular canals, otolith organs, spatial orientation, navigation

The survival of most species depends on the ability to navigate accurately within the environment. Accurate navigation depends on neural representations for location and direction, as well as distance traveled. These spatial signals are encoded by place cells, grid cells, border cells, and head direction (HD) cells (O'Keefe and Nadel, 1978; Taube, 2007; Moser et al., 2008; Lever et al., 2009). It is well known that external (allothetic) visual cues dominantly control these representations, but self-movement (idiothetic) cues can gain control when familiar visual cues are unavailable (O'Keefe and Conway, 1978; Hill and Best, 1981; Muller and Kubie, 1987; O'Keefe and Speakman, 1987; Quirk et al., 1990; Goodridge and Taube, 1995; Taube and Burton, 1995; Yoder et al., 2011a). These idiothetic cues include neural representations of the rate of linear movement through the environment, as well as the rate and direction (clockwise vs. counter-clockwise) the head is turning (McNaughton et al., 1989; Bassett and Taube, 2001; Sharp et al., 2001; Jacobs et al., 2010). Some of this information appears to originate in the vestibular system, and recent studies provide insight into the role of vestibular signals in spatial functions. This review therefore focuses on the contribution of vestibular information to navigation and the allocentric spatial signals in animals, with a primary emphasis on the HD signal in rodents.

VESTIBULAR INVOLVEMENT IN NAVIGATION: BEHAVIORAL STUDIES

The vestibular system includes the semicircular canals and otolith organs, which sense angular and linear acceleration, respectively. At first glance, this self-movement information would not appear to be necessary for navigation under light conditions, given the predominant reliance on visual cues. However, humans with bilateral vestibular dysfunction are impaired at virtual navigation tasks, suggesting vestibular signals are necessary for navigation even in purely visual environments (Brandt et al., 2005). A more recent study found that humans were able to accurately use self-motion cues to accurately update their perceived orientation during active walking or passive transport, but were impaired when they walked in place (Frissen et al., 2011). This finding suggests that the vestibular detection of head movement is the critical factor in the perception of orientation in this task, given that motor efference signals would have been present during walking in place. The reader should consult Israël and Warren (2005) for a review of studies using human subjects that examines the role of the vestibular system in spatial orientation. A vestibular contribution to spatial signaling has also been found in non-human primates. For example, inertial motion influenced the activity of approximately two-thirds of the dorsal medial superior temporal area (MSTd)

Table 1 | Effects of vestibular system manipulations on navigation and spatial signals in rodents.

Type	Manipulation	Result	Reference
Behavior	Vestibular nerve cauterization	Impaired T-maze alternation	Potegal et al. (1977)
	Vestibular nuclei lesion	Impaired return from passive transport	Miller et al. (1983)
	Passive rotation	Impaired working and reference memory (water maze)	Semenov and Bures (1989)
	Sodium arsanilate	Impaired working memory (radial maze)	Ossenkopp and Hargreaves (1993)
	Labyrinthectomy	Impaired reference memory (radial maze)	Russell et al. (2003a)
	Sodium arsanilate	Impaired navigation w/o visual cues (square arena)	Stackman and Herbert (2002)
	Sodium arsanilate	Impaired food-hoarding (homing) in darkness	Wallace et al. (2002)
	Vestibular aspiration	Impaired food-hoarding (homing) in darkness	Zheng et al. (2009)
	Slow rotation	Impaired pup retrieval (homing) in darkness	Mittelstaedt and Mittelstaedt (1980)
	Vestibular ablation + passive rotation	Impaired spatial discrimination (radial maze)	Matthews et al. (1989)
	Sodium arsanilate	Impaired working and reference memory (radial maze); impaired Y-maze alternation	Besnard et al. (2012)
	Utricle dysfunction	Impaired movement in darkness	Avni et al. (2009)
	Otolith dysfunction	Impaired working and reference memory (radial maze)	Kirby and Yoder (2012)
	Otolith dysfunction	Impaired place recognition (Y-maze)	Machado et al. (2012)
Electrophysiology	Labyrinthectomy	Attenuated hippocampal theta rhythm	Russell et al. (2006)
	Passive rotation	Induced theta rhythm	Shin (2010)
	Passive rotation	Induced theta rhythm	Tai et al. (2012)
	Sodium arsanilate	Eliminated HD signal	Stackman and Taube (1997)
	Tetrodotoxin	Eliminated HD and place cell signals	Stackman et al. (2002)
	Labyrinthectomy	Eliminated place cell signal	Russell et al. (2003b)
	Inverted orientation in microgravity	Eliminated HD signal	Taube et al. (2004)
	Microgravity (space flight)	No effect on place cell activity	Knierim et al. (2000)
	Inverted navigation	Disrupted HD signal	Calton and Taube (2005)
	Otolith dysfunction	Degraded HD signal	Yoder and Taube (2009)
	Passive rotation	Post-rotational activation of HD cell	Taube (2004) Barany Society Meeting (Figure 2)
	Plugged semicircular canal	Eliminated directional tuning of HD cells	Muir et al. (2009)
	Absence of horizontal canals	Absence of HD cells	Taube and Valerio (2012)

neurons that responded to optic flow cues, but this influence was absent in animals with bilateral vestibular lesions (Gu et al., 2007). Additionally, numerous rodent studies over the past few decades (**Table 1**) indicate that vestibular signals do influence landmark navigation, suggesting that visual information alone is not sufficient for accurate spatial performance. One possibility is that vestibular lesions disrupt behavior by eliminating the vestibulo-ocular reflex (VOR), which could affect visual acuity during active locomotion. However, if this were the case, we would expect deficits on tasks that require navigation relative to distal visual cues. This deficit does occur for some tasks, but intact landmark navigation has been reported in vestibular lesioned animals (e.g., Stackman and Herbert, 2002; Wallace et al., 2002). It is therefore unlikely that the behavioral deficits described below are attributed to the loss of the VOR.

Vestibular involvement in rodent navigation is indicated by spatial deficits following vestibular system lesions or stimulation. One study investigated spontaneous alternation in rats that received bilateral cauterization of the vestibular nerve (Potegal et al., 1977). Spontaneous alternation is the behavior displayed by

animals performing a repetitive T-maze task where both left and right arms are always baited for each trial. The animals normally alternate their choices on each trial between the two arms (left vs. right), and impairments are indicated by repeated entries to the same arm. This study used Douglas's (1966) two-maze procedure, where two identical T-mazes were positioned parallel to one another in different rooms. Vestibular lesioned animals showed profound impairments relative to control groups, suggesting an important vestibular contribution on the performance of this spatial task. Another study confirmed the vestibular system's role in navigation performance with a "return from passive transport" task that involved transporting water-deprived rats to points at increasing distances from a water spout, and then evaluating their ability to return directly to the start point (Miller et al., 1983). Blinded rats and those that received cerebellar cortex lesions were able to return successfully from greater distances than rats with lesions of the vestibular nuclei, although the vestibular lesioned animals performed better than predicted by chance.

Activation or lesion of the vestibular system also appears to disrupt spatial learning on tests of spatial working (within-trials) and reference (across-trials) memory. A period of rotation immediately before retrieval trials or after acquisition trials failed to disrupt the ability to find the platform location on working and reference memory versions of a water maze task, although post-rotatory effects increased escape latency (Semenov and Bures, 1989). However, when animals were rotated for 30 s while they were on the platform, the rotation disrupted later retrieval only when distal visual cues were available, suggesting vestibular activation can disrupt the use of spatial cues for navigation. Another study showed that transtympanic injections of sodium arsanilate, which destroys vestibular hair cells, impaired spatial working memory on an eight-arm radial maze, as indicated by greater latency and more revisits to arms (Ossenkopp and Hargreaves, 1993). The vestibular system is also important for spatial reference memory on the radial arm maze, as rats with bilateral vestibular lesions were impaired at finding a single baited arm (Russell et al., 2003a). A recent study confirmed the vestibular involvement in spatial learning, showing increased working and reference memory errors on the radial maze and reduced spontaneous alternation on a Y-maze following bilateral sodium arsanilate injections to the vestibular labyrinth (Besnard et al., 2012). Together, these results suggest that, despite the predominant reliance on visual cues, the vestibular system provides a necessary signal that complements visual information during landmark navigation.

In the absence of familiar landmarks, navigation is guided by self-movement cues including motor efference copy, optic flow, proprioception, or vestibular signals. Several tasks have been used to test the importance of the vestibular contribution to this type of navigation. The food-hoarding task requires animals to exit a start box and explore a circular table in search of food and, upon finding the food, carry it directly back to the start box where the food is consumed. This "homing" task is often conducted in both light and darkness; the ability to return directly to the start box in light is thought to involve landmark navigation whereas the direct return in darkness is thought to require an online record of self-movement cues throughout the outbound journey. Vestibular involvement in this form of navigation is indicated by impaired homing in darkness in rats with bilateral sodium arsanilate injections into the vestibular labyrinth (Wallace et al., 2002). Vestibular lesioned and control rats performed similarly in light, whether the start location was cued or hidden. However, vestibular lesioned rats were markedly impaired in darkness, suggesting the vestibular signals are critical for non-visual navigation. A later study confirmed these findings, and further demonstrated that the effects of vestibular dysfunction persist for at least 5 months after the lesion (Zheng et al., 2009). Importantly, the initial heading angle for control rats showed a preference for the correct angle, whereas vestibular lesioned rats did not show this preference. This error in initial heading suggests impaired angular path integration, which is thought to depend on the HD signal (discussed in Section "HD Signal Involvement in Navigation – Electrophysiology and Behavior"). Although the homing task's sole reliance on self-movement information has been questioned, a study confirmed that self-movement cues can indeed guide navigation on this type of homing task (van der Meer et al., 2010). In their experiment rats had to traverse a circular table to a central platform, after which the table or central platform was rotated in order to displace the original start location relative to the rat. After this rotation the rats had to return to their initial starting location. For most rotation trials, the return trip led to a location that was consistent with the rotation, instead of to the original location as defined by allocentric cues. This result confirms the use of self-movement cues for homing, and the fact that vestibular lesioned rats were impaired on homing tasks, provides strong evidence for a vestibular contribution to non-visual navigation. Further, the vestibular system appears to contribute to navigation performance on relatively simple navigation tasks. Bilateral sodium arsanilate injections to the vestibular labyrinth impaired rats' ability to find a water cup that was consistently located in one corner of a square arena when visual landmarks were absent (Stackman and Herbert, 2002). When visual landmarks were available, however, vestibular lesions did not disrupt the ability to find the water cup. Thus, we currently have considerable evidence that the vestibular system provides some of the idiothetic cues that guide navigation when familiar visual landmarks are not available.

The results of navigation tests following complete vestibular lesions clearly indicate an important role for the vestibular system in both visual and non-visual navigation, but the specific type of vestibular contribution (rotational vs. linear movement) cannot be gained from these studies. Spatial deficits in animals with bilateral labyrinthectomy could have resulted from impaired sensation of gravity, translation, or rotation, given that signals from both the otolith organs and semicircular canals were eliminated in lesion studies. An early study indicated that the semicircular canals contribute to the ability of female gerbils to collect their pups and carry them directly back to the nest in complete darkness (Mittelstaedt and Mittelstaedt, 1980). When the dam was slowly rotated (acceleration $\leq 0.24°/s^2$) to an angular displacement of 37° after arriving at the pups' location, the return trip deviated by a similar angle. However, rapid rotation did not impair the direct return to the nest, suggesting the semicircular canals detected the rapid rotation and allowed her to correct for the rotation. Additional evidence for a vestibular contribution to non-visual

navigation comes from a study that used a six-arm radial maze where rats could be rotated between trials (Matthews et al., 1989). When the center platform was rotated in the absence of landmark cues, control rats were able to detect the passive rotation and choose the correct arm, whereas vestibular lesions impaired this ability. The addition of visual landmark cues improved performance somewhat for the vestibular group, but only partially compensated for the loss of vestibular signals. These findings thus suggest that signals from the semicircular canals contribute significantly to navigation, but they do not address the possible otolithic contribution.

Several recent studies have tested the otolithic contribution to navigation by using genetically modified mice that lack functional otolith organs. One study evaluated the open-field behavior in darkness of *headbanger* mice, which have a congenital malformation of the stereocilia in the utricle (Avni et al., 2009). Control animals typically traveled over long paths and visited many parts of the arena, whereas *headbanger* mice typically made many short movements, followed by a return to the start location. In contrast, control mice moved throughout the arena in relatively continuous journeys, thus visiting more zones than *headbanger* mice. This finding suggested that the *headbanger* mice had impaired path integration – the navigational process by which animals update their spatial orientation by continuously monitoring their movement cues (e.g., vestibular, proprioceptive, motor efference, optic flow). Interestingly, and somewhat surprisingly, a recent study showed that the otolith organs also contributed to navigation when it required the use of visual extramaze cues (Kirby and Yoder, 2012). Across days, homozygous *tilted* mice showed more spatial working and reference memory errors on a radial arm maze discrimination task than their heterozygous littermates when only extramaze cues were available, but performed as well as control mice when visible intramaze cues were available to signal the goal locations. Together, these two studies suggest the otolith organs contribute to spatial performance under both dark and light conditions. However, the fact that *tilted* mice were not impaired at cued navigation on a radial maze suggests they were able to recognize locations when local cues were available. One possibility is that these navigation deficits resulted from impaired place recognition, which was recently demonstrated in otoconia-deficient *head tilt* mice (Machado et al., 2012). The navigation deficits in animals with otolith dysfunction thus appear to be specific to tasks that require the use of distal or self-movement cues. However, whether these deficits resulted from the lack of otolith signals or from changes to the semicircular canal-mediated signals is not known at the present time, given that congenital otolith deficiency may alter canal-mediated signals (Beraneck and Lambert, 2009). The canals and otolith organs provide convergent input to many neurons in the medial vestibular nuclei (Bush et al., 1993), and the lack of otolith input could produce altered responses in these cells. If true, canal-dependent functions such as the VOR could also be altered. This possibility was confirmed by a study using *head tilt* mice, which have dysfunctional otolith organs (Harrod and Baker, 2003). Nevertheless, the use of mice with dysfunctional otolith organs in spatial tasks provides important insight that is not possible to obtain from other models.

VESTIBULAR PATHWAYS TO SPATIAL FUNCTIONS

HIPPOCAMPAL THETA RHYTHM

Several studies have shown that vestibular signals may influence navigation via their involvement with hippocampal theta rhythm. First, rats with sodium arsanilate-induced vestibular lesions performed as poorly on the radial arm maze task as rats with hippocampal lesions, but animals with combined vestibular/hippocampal lesions did not perform worse than either lesion alone, suggesting the vestibular contribution to spatial performance may arrive via hippocampal circuits (Allen et al., 2007). This suggestion is consistent with the finding that vestibular lesions attenuate hippocampal theta rhythm – a robust field potential oscillation associated with sensory and movement processing (Bland and Oddie, 2001; Russell et al., 2006). Second, passive rotation induced continuous theta rhythm in rats and mice (Gavrilov et al., 1995; Shin, 2010) via the activation of cholinergic septohippocampal cells (Tai et al., 2012). It is important to note, however, that the attenuation of movement-related theta rhythm alone, which can result from selective cholinergic or GABAergic lesions in the medial septum (Lee et al., 1994; Yoder and Pang, 2005), is not sufficient to impair spatial learning, as landmark navigation remained mostly unaffected on a water maze and radial arm maze following either of these lesions (Berger-Sweeney et al., 1994; Torres et al., 1994; Baxter et al., 1996; Pang et al., 2001; for review, see Parent and Baxter, 2004). Further, a recent study demonstrated that theta-paced stimulation alone could not restore vestibular lesion-induced impairments in a spatial non-matching-to-sample task (Neo et al., 2012). These results suggest that theta rhythm normally includes more than just vestibular information, although the vestibular content of theta rhythm is not well understood at the present time. However, it remains possible that vestibular information is conveyed by both theta rhythm and the HD signal, and both of these signals are necessary for normal spatial performance (discussed in Section "Spatial Signals"). Both the ascending theta and HD cell circuits originate in the tegmental region – which receives vestibular signals – and include many of the same nuclei, albeit different subregions (for review, see Vertes et al., 2004). Future studies focusing on the vestibular involvement in hippocampal physiology and spatial signals will undoubtedly provide important advances in our understanding of the sensory signals that contribute to spatial functions.

SPATIAL SIGNALS

The vestibular system may contribute to spatial performance via its influence on generating various spatial signals. The pathway that conveys vestibular information to the hippocampus and place cells is not well known, but we have a much better understanding of the vestibular pathway to the HD cell circuit. Generation of the HD signal is thought to occur within the reciprocal connections between the dorsal tegmental nuclei (DTN) and lateral mammillary nuclei (LMN), based on the representation of angular head velocity, which the DTN receives from the vestibular nuclei via the supragenual nucleus and the nucleus prepositus (Lannou et al., 1984; Brown et al., 2005; Song and Wang, 2005; Biazoli et al., 2006). Once generated, the HD signal is projected bilaterally via the mammillothalamic tract to the anterior dorsal thalamus (ADN), which then projects to the postsubiculum (PoS;

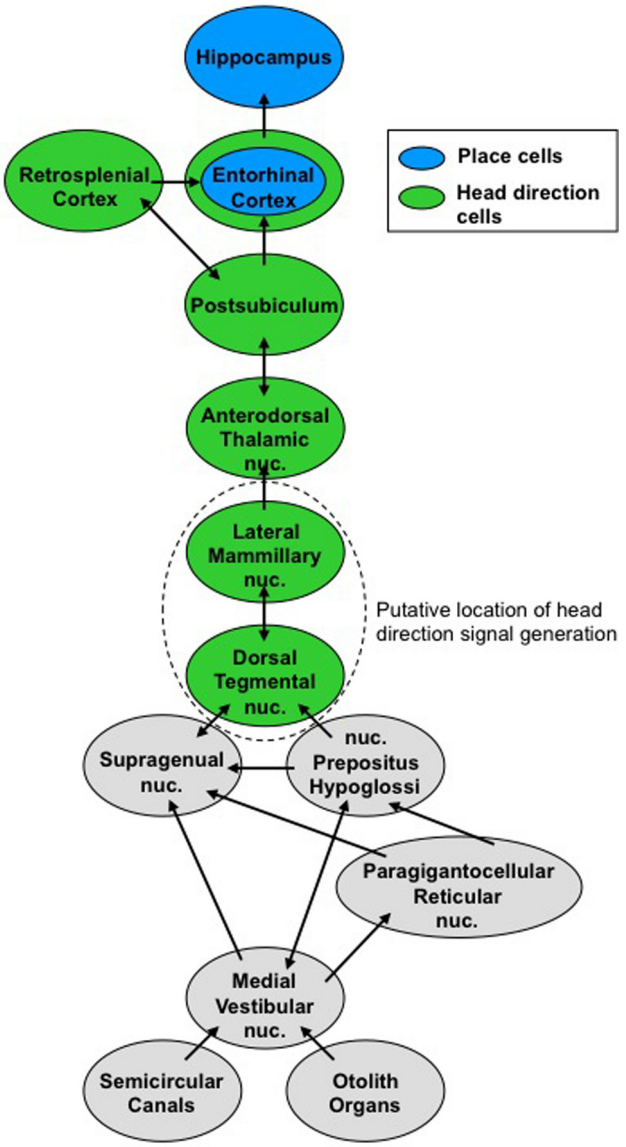


FIGURE 1 | Vestibular pathways to the ascending head direction cell circuit. Signals from the semicircular canals and otolith organs converge on the medial vestibular nuclei. This vestibular information contributes to the head direction signal, which ascends to brain regions involved in navigation.

also referred to as dorsal presubiculum). In turn, the PoS projects to the entorhinal and retrosplenial cortical areas (**Figure 1**). This view is supported by studies that demonstrated complete loss of the HD signal in the ADN after lesion of the DTN or LMN (Blair et al., 1999; Bassett et al., 2007; Sharp and Koester, 2008), and loss of direction-specific firing in PoS cells after lesion of the ADN (Goodridge and Taube, 1997). Given the known efferent connections of the PoS (van Groen and Wyss, 1990b), the HD signal in entorhinal and retrosplenial cortical areas presumably depends on input from the PoS and/or the ADN, although no data are available to support this notion. Additionally, vestibular information may reach high-level brain regions via other pathways, such as the ascending vestibular projections to the ventral posterior thalamus, which then projects to the parietal insular vestibular cortex (PIVC; for review, see Shinder and Taube, 2010). This pathway shares information involving proprioceptive somatic cues and may be more involved with postural awareness – particularly in distinguishing active head movements from head movements that accompany body movements. To date, this pathway has not been identified in rodents, but unilateral or bilateral parietal cortex lesions disrupt spatial performance on some tasks (Crowne et al., 1992; Kolb et al., 1994; McDaniel et al., 1995), and parietal cortical neurons are known to represent route-based information that may contribute to spatial task performance (Nitz, 2006, 2009). Further, human studies have revealed an important interaction between the parietal cortex and hippocampus during allothetic cue processing (Zhang and Ekstrom, 2013). Nevertheless, if these pathways do contribute to spatial performance, they occur separately from the HD signal because lesions of the parietal cortex do not disrupt the HD signal within the limbic system (Calton et al., 2008). Thus, at least a portion of the vestibular contribution to navigation appears to arrive at high-level brain regions via the HD signal, whereas the other ascending vestibular pathways most likely contribute to other functions, such as postural awareness.

The importance of the vestibular system in contributing information to various types of spatial signals has been well demonstrated both directly and indirectly (**Table 1**). One of the first studies showed that the HD signal was disrupted by bilateral lesions of the vestibular labyrinth (Stackman and Taube, 1997). The authors were unable to identify any HD cells in the ADN in rats that had previously received bilateral injections of sodium arsanilate into the vestibular apparatus. An additional inactivation study confirmed these results and further demonstrated vestibular involvement in the activity of hippocampal place cells (Stackman et al., 2002). This study recorded HD cells in the PoS and place cells in hippocampus, after which tetrodotoxin was injected bilaterally into the vestibular apparatus. Post-injection recordings showed that this temporary vestibular inactivation disrupted the HD and place cell signals for several days, after which the signals recovered. The loss of location-specific activity in hippocampal place cells after removal of vestibular signals was confirmed in rats following permanent bilateral vestibular lesions (Russell et al., 2003b). Interestingly, the vestibular contribution to the place cell signal does not appear to be conveyed exclusively via the HD signal, as lesions of the ADN (Calton et al., 2003) or LMN (Sharp and Koester, 2008) impaired the stability of hippocampal place cells, but did not disrupt their location-specific activity. Nevertheless, these studies indicate an important role of the vestibular system in generating both place and HD cell signals.

Additional studies have indirectly confirmed that vestibular signals contribute to the HD signal. One study evaluated HD and place cell activity when self-movement cues and visual landmarks were in conflict (Knierim et al., 1998). Both HD and place cells were predominantly controlled by visual landmarks when the conflict was small, but self-movement cues provided the greatest influence when the conflict was large. In normal situations where self-movement and visual cues are not in conflict, discrete visual landmarks often predominantly control the HD signal (Goodridge and Taube, 1995). However, in the absence of discrete cues, the

HD signal can be controlled by geometric information – which serves as a landmark – or by self-movement cues. When rats were permitted to actively explore asymmetric environments, the HD signal was controlled by self-movement cues instead of geometry (Knight et al., 2011). However, when rats were passively disoriented between trials, HD cells were predominantly controlled by geometric cues (see also Clark et al., 2012b). Given the vestibular involvement in path integration and the HD signal, at least a portion of the self-movement information that controls the HD signal likely originates in the vestibular system. Overall, the results of lesion studies, disorientation studies, and cue conflict studies demonstrate an important role for vestibular representations in both place cell and HD cell signals.

The loss of spatial signals after elimination of vestibular information suggests that spatial signals depend on information from the otolith organs or semicircular canals, or both. The first study to address which component of the vestibular system might be important was an experiment recording from hippocampal place cells on the Neurolab space shuttle mission, where the microgravity (0-*g*) environment causes reduced gravitational activation of the otolith organs (Knierim et al., 2000). The microgravity environment was found to have minimal effect on place cells as rats navigated a three-dimensional track. This finding suggests that otolith signals are not necessary for generating place cell activity, at least in terms of providing a tonic gravitational signal. The otolith organs, of course, would have detected translatory movements in the 0-*g* environment, and this representation of translation may therefore have provided a critical component of the place cell signal. However, a recent study suggests that place cell firing can persist in virtual navigation, despite the absence of translation and associated activation of the otolith organs (Chen et al., 2013). This finding suggests that the representation of translation is not necessary for place cell function, although the number of complex spike cells that fired in a location-specific manner was reduced in virtual navigation, relative to real-world navigation in a similar environment. Real-world translation may therefore contribute to the place cell signal, but no previous studies have shown whether this contribution depends specifically on the otolith organs. To address this issue, we recently recorded from hippocampal cells in otoconia-deficient *tilted* mice and found a small number of relatively normal place cells while the mice foraged in an open field, suggesting the otolith organs are not necessary for the place cell signal (Yoder et al., 2014 Midwestern Psychological Association). Aside from these studies, no evidence is currently available to disambiguate the otolith and canal contributions to the place cell signal.

Other experiments have addressed the otolithic contribution to the HD signal. One study evaluated the effects of microgravity on HD cell activity by recording from rats during parabolic flight (Taube et al., 2004). HD cells remained directional when rats navigated on the floor during 0-*g*, suggesting the otolithic representation of gravity is not crucial for the HD signal. However, if the animal was passively moved to the walls or ceiling of the apparatus the directional signal was lost, suggesting that the representation of gravity contributes to reorientation when the plane of locomotion changes. It is also possible that this HD signal instability occurs only during passive displacement in conditions where the lack of gravity detection prevents constant monitoring of body orientation. This issue was later addressed by a study in 1-*g* on Earth that monitored HD signal activity during active locomotion in upright, pitched, and inverted positions (Calton and Taube, 2005). Rats were trained to shuttle from one compartment of an apparatus located on the floor, up a wall, along the underside of the ceiling, and down the opposite wall into a second compartment of the apparatus, after which the animals reversed direction to shuttle back to the original start compartment. During this journey, many HD cells remained directional when the rat ascended the first wall but lost their directional tuning when the rat became inverted on the ceiling, only to regain directionality when the rat descended the second wall to reach the goal compartment on the floor. We have since confirmed that HD cells lose their directional firing during inversion using a different spatial task. In this task rats had to find an escape hole while walking inverted along the underneath side of a large suspended circular platform (Gibson et al., 2013). This loss of directional firing during inversion may have resulted from an unfamiliar otolith signal, given that inversion is rarely experienced by terrestrial lab rats. Importantly, along with the parabolic flight experiment, this result indicates that HD signal degradation occurs during inversion, regardless of whether the animal is actively or passively displaced and whether the animal is in a 0-*g* or 1-*g* environment. More recently, a complementary test of the otolithic contribution to the HD signal used mice lacking functional otolith organs (Yoder and Taube, 2009). HD cells in *tilted* mice were robustly directional during the initial recording session, but became progressively degraded across trials. Additionally, many non-directional "bursty" cells were present in *tilted* mice during recording sessions when no HD cells were found. This bursty pattern was similar to that of HD cells, which show bursts of activity when the head is pointed in a particular direction, although the activity of bursty cells failed to reliably occur while the head was pointed in only one direction. These bursty cells may therefore have been HD cells that failed to maintain precise directional tuning. Nonetheless, the HD signal degradation of *tilted* mice may have resulted from the absence of a subjective vertical, which appears to depend on the detection of gravity (Mittelstaedt, 1986). Thus, the loss of otolithic signals is detrimental to the HD signal, but does not account for the entire effect of vestibular lesions on the HD signal. It is therefore possible that the semicircular canals provide the information crucial to HD signal generation.

Involvement of the semicircular canals in the HD signal is indicated by several recent studies. **Figure 2** presents data from our laboratory demonstrating that HD cells respond with periodic bursts of firing following post-rotational spinning of the rat (Taube, 2004 Barany Society Meeting). First, a typical HD cell in the ADN was recorded while the rat foraged for food within a cylinder containing a prominent visual cue card (**Figure 2A**). Then the rat, which was free to move on a 1-m diameter platform, was spun continuously in the dark in one direction for about 1 min at constant speed (∼30–50 rpm). The rat generally remained motionless during the rotational period and did not move or turn its head. After a few seconds of rotation, there was a loss of direction-specific firing in the HD cell, although the cell was not quiescent, but

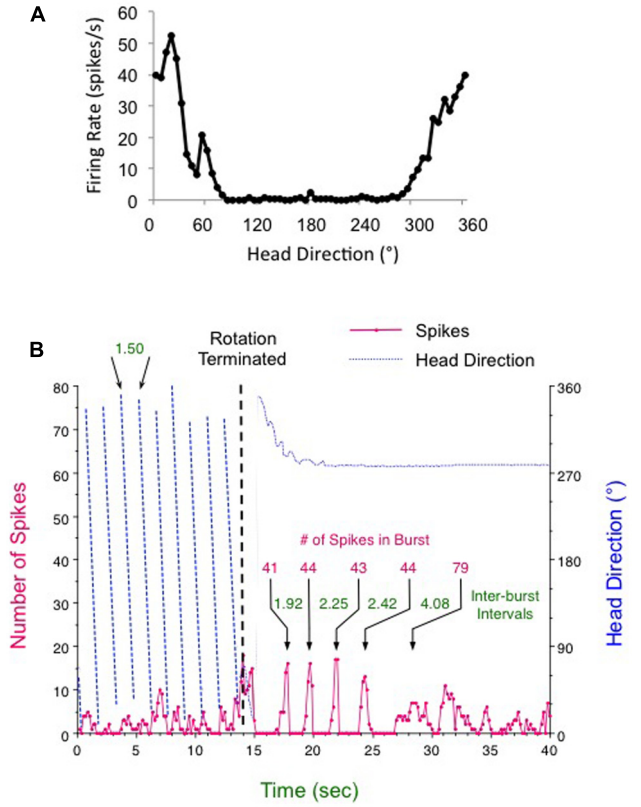


FIGURE 2 | Head direction cell responses following (A) an active foraging session in the cylinder and (B) continuous clockwise rotation for 1 min (only the final 14 s are shown) followed by abrupt braking (vertical dashed line). After termination of rotation the HD cell fired in five periodic bursts over about 10 s. For this post-rotation period the amount of time in between each burst increased over each interval (times denoted in green for each inter-burst interval), although the number of spikes composing each burst (denoted in red) was about the same – particularly for the first four bursts. See text for further details.

appeared to fire at random directions leading to an elevated background firing rate (see **Figure 2B**, pre-brake period red line). The loss of directional tuning was presumably due to the disoriented state of the animal as a result of the continuous rotations. The platform was then stopped abruptly (**Figure 2B**, vertical dashed line) while cell recording continued during the post-rotational period. During the post-rotational period the rat initially moved for the first 3 s (14–17 s time points, see blue dotted line in **Figure 2B**) and then remained motionless over the next 23 s. The red line in **Figure 2B** shows that the cell's response during the rotational period (from 0 to 14 s) occurred at a relatively steady low firing rate that was generally non-directional. The firing rate during this period was greater than the background firing rate (0.378 spikes/s) of the cell during an active foraging session without any spinning (**Figure 2A**). Once the rotation was stopped at the 14 s time point, the cell responded by going through an initial burst of firing (at the 14–15 s time point), which was followed by five periods of burst firing (between the 15–25 s time points). Interestingly, each burst contained about the same number of spikes (∼44) and lasted about 666 ms. The period in between each burst was marked by the absence of firing and the interburst interval increased in a linear manner ($r = 0.992$) over 10 s. Following the 13 s post-rotational period, the cell's firing rate became more variable and was somewhat increased compared to the period during the rotational spinning. After ∼1 min, the cell's firing pattern returned to normal and was once again directional (data not shown). These data suggest that the HD signal can be heavily influenced by canal activation, which would have occurred when the canal's cupula was deflected by the inertial movement of the endolymph fluid after the head rotation had stopped abruptly. The cupula's deflection would have activated vestibular hair cells and led to a response that was propagated forward and affected the HD cell network to the extent that the animal perceived it was spinning (in the opposite direction) and the recorded HD cell was activated periodically – once for each revolution through the cell's preferred firing direction. The increasing interval between each burst was most likely due to the slowing of the endolymph fluid over time. Similar responses are seen with ocular nystagmus following termination of continual rotation (Leigh and Zee, 2006). Although this response did not occur in every animal every time the animal was rotated, the fact that it can occur demonstrates the importance of the vestibular system in generating the HD cell signal.

Other studies in animals with dysfunctional canals have confirmed the canals' role in HD signal generation. One study used chinchillas, which have large vestibular apparatus that can be accessed easily during surgery, to determine whether removal of the canals would affect the HD signal (Muir et al., 2009). HD cells similar to those of rats were recorded from the chinchilla ADN prior to a surgery in which the horizontal, superior + posterior, or all three semicircular canals were plugged bilaterally, rendering the respective canals dysfunctional. After surgery, cells recorded within the ADN were no longer directionally tuned, suggesting the canals provide input that is crucial to the HD signal. Findings consistent with these results were provided by a study using *epistatic circler* (*Ecl*) mice, which have a genetic mutation that causes them to develop without horizontal canals – control mice exhibited normal HD cells, but no HD cells were detected in the ADN of *Ecl* mice (Taube and Valerio, 2012). Importantly, in both canal-plugged chinchillas and *Ecl* mice, many animals showed bursty cells similar to those of *tilted* mice. These would-be HD cells therefore appear to be able to maintain their basic firing properties, but lack the input necessary to maintain their directional specificity over time. This interpretation is quite plausible, given that the canals represent changes in angular head position along the horizontal plane, which would move the head from one direction to another. This direct coupling between the canals and the generative portion of the HD circuit may therefore be akin to the coupling between the canals and VOR circuit and presumably involves a mathematical integration in time to derive angular head displacement (i.e., a change in HD) from the angular head velocity signal that is ubiquitous throughout vestibular brainstem pathways. Whether the nucleus prepositus, which is critically involved in the mathematical integration for the VOR, is also involved in the mathematical integration for the HD system is not known. Preliminary studies, however, have shown that lesions of the nucleus prepositus disrupt the HD signal (Butler and Taube, 2012). Other possibilities include the supragenual nucleus, which lies anatomically adjacent to the

medial vestibular nuclei, and is also known to be a critical structure for generating the HD signal (Clark et al., 2012). Finally, a preliminary study reported that velocity storage, the prolonged vestibular signal within the vestibular nuclei that outlasts the afferent sensory signal, contributes to stable HD representations. Taube and Bassett (2005) found that disrupting velocity storage, by severing the commissural connections between the two vestibular nuclei, resulted in a constant under-signaling of angular head velocity at high frequency head turns. In turn, this effect led to a distorted HD signal where the animal's perceived directional heading consistently lagged behind its true (actual) heading. This occurrence was manifested by the HD cell shifting its preferred direction ahead as the animal moved through the environment.

Overall, the vestibular system is known to contribute to theta rhythm, place cells, and HD cells, but it is also possible that theta rhythm directly influences these spatial representations. The relation between theta rhythm and place cell activity is well known, with place cells showing "phase precession," or a tendency to fire at increasingly earlier phases of the theta cycle as the animal walks through a cell's place field (O'Keefe and Recce, 1993). In contrast, HD cells in the ADN, as well as the LMN and PoS, do not show theta phase precession, and an interspike interval analysis of these cells did not reveal theta rhythmic modulation (Taube, 2010). However, some HD cells in the anteroventral thalamus (AVN) did show theta modulation, suggesting a relation between theta rhythm and HD cells in some brain areas (Tsanov et al., 2011). This theta modulation may arrive at AVN via a direct projection from the medial mammillary nuclei, where many angular head velocity cells are strongly modulated by theta rhythm (Sharp and Turner-Williams, 2005). Theta modulation of HD cell activity has also been observed in the entorhinal cortex, with some HD cells firing preferentially on alternate theta waves (i.e., "theta skipping"), while other HD cells within the same region fail to show this firing pattern (Brandon et al., 2013), suggesting that there are different types of HD cells within the entorhinal cortex. Theta skipping is known to occur throughout the entorhinal cortex (Deshmukh et al., 2010), but the significance of this phenomenon is not known at the present time. Thus, theta rhythm is heavily involved in place cell function, but its influence on the HD signal is less pronounced and is not found throughout the HD cell circuit.

HD SIGNAL INVOLVEMENT IN NAVIGATION – LESION STUDIES

The vestibular system is necessary for both the HD signal and navigation, suggesting that the HD signal may convey vestibular information to higher cortical navigation centers. If true, disruption of the HD signal at any point along the ascending HD circuit (DTN → LMN → ADN → PoS) would impair navigational performance. This proposal has been confirmed by lesion and inactivation studies using various spatial tasks.

DORSAL TEGMENTAL NUCLEI

N-methyl-D-aspartate (NMDA) lesions of the DTN impaired both landmark navigation and path integration on a food-carrying task where sighted or blindfolded rats walked from a refuge into an open field, foraged for large food pellets in the open field, and then carried the food back to the refuge for consumption (Frohardt et al., 2006). This study evaluated task performance after DTN or ADN lesions, and found that the greatest impairment was seen in the DTN lesioned animals, both with and without blindfolds. DTN involvement in spatial functions was recently confirmed with DTN lesion-induced impairments on a water T-maze task that required rats to choose the direction that led to an escape platform, as well as on a food-foraging task in light (Dwyer et al., 2013). Additionally, in a recent study that manipulated various local and distal cues in the water maze task, DTN lesions increased the number of trials it took the rats to reach criterion and impaired their ability to navigate accurately to a place in absolute space, relative to a set of stable distal landmarks (Clark et al., 2013). Interestingly, the DTN lesioned animals were not impaired on the water task when the pool was repositioned at the start of a trial, but the platform was placed in the same relative position within the pool. Thus, despite the absence of an HD signal, the rats were still capable of swimming in the proper direction relative to cues located within the pool.

LATERAL MAMMILLARY NUCLEI

The other region of the HD generator, the lateral mammillary nuclei, is also necessary for navigation. Mammillary lesions impaired reinforced T-maze alternation and impaired the use of spatial cues in a cross-maze and a radial-arm maze, but did not impair performance on an egocentric discrimination task (Neave et al., 1997). Another study showed that neurotoxic mammillary, as well as anterior thalamic and fornix lesions, disrupted forced and continuous T-maze alternation (Aggleton et al., 1995). A series of studies confirmed these results, with mammillary (and anterior thalamic) lesions impairing performance on a radial arm maze, but not an egocentric conditional associative learning task (Saravis et al., 1990; Sziklas and Petrides, 1993, 2000, 2004; Sziklas et al., 1996; for review, see Sziklas and Petrides, 1998). LMN lesions also moderately impaired performance on a water maze task, although the deficits tended to be transient and were not as great as when the entire mammillary nuclei, including the medial mammillary nuclei, were lesioned (Vann, 2005). The fiber tract that conveys the mammillary signal to the thalamus is also critical for spatial performance, as lesion of the mammillothalamic tract or mammillary bodies impaired forced alternation on a T-maze, and impaired radial arm maze and water maze performance (Vann and Aggleton, 2003). A more recent study demonstrated that mammillothalamic tract lesions disrupt performance on a food-hoarding task that requires path integration and the processing of self-movement (idiothetic) cues for accurate performance (Winter et al., 2011).

ANTERODORSAL THALAMUS

As one would predict, the ADN, which receives the HD signal from LMN (Blair et al., 1999; Bassett et al., 2007), is also involved in navigation. NMDA lesions of the entire anterior thalamic region impaired radial arm maze performance as well as allocentric cue-based alternation and forced alternation on a T-maze, but did not impair egocentric alternation (Aggleton et al., 1996). This study also evaluated performance as a function of the lesion extent, with groups having damage limited to the anteromedial nuclei or the anterodorsal/anteroventral nuclei. Neither group showed impaired allocentric alternation on the cross-maze, but the

anteroventral/anterodorsal group was impaired on the radial maze task. Anterior thalamic lesions also impaired place learning, but not visual discrimination, on a water maze task (Moreau et al., 2013).

In finding the hidden platform in a water maze task, an animal can rely on the absolute reference frame of the room as indicated by distal room cues – mostly visual landmarks along the walls of the surrounding room, or on the relative reference frame, which is based more on the local, intramaze cues, such as the distance between the apparatus wall and the platform. A recent study in mice reported that the ADN played an important role in processing local cue information (Stackman et al., 2012). Examination of the swim paths of male control mice indicated that the animals relied on pool-based cues (relative reference frame) over extramaze cues (absolute reference frame) on a probe test that did not contain the platform. However, rotation of the extramaze cues led to a corresponding shift in the trajectories the mice took when released into the pool, suggesting that both pool- and room-based reference frames were used to guide behavior in the search for the hidden platform. Disorienting the mice before placement in the water disrupted their reliance on pool-based cues and responding to a relative reference frame. Mice that had their anterior thalamic nuclei inactivated showed a preference for using an absolute reference frame strategy. In contrast, dorsal CA1 region inactivation did not disrupt the preference for the relative reference frame (intramaze cues). Taken together, these results suggest that the anterior thalamic nuclei play an important role in guiding behavior based on the relative, local cue-based reference frame, as opposed to a strategy based on the absolute, distal-cue based reference frame. Because the PoS has been suggested to be the route by which landmark information is conveyed to the hippocampus (Goodridge and Taube, 1997; Yoder et al., 2011b), it is possible that inactivation of the anterior thalamic nuclei would not interfere with the information transfer of distal landmark information to the hippocampus – thus, leaving intact the absolute reference frame-based strategy that was evident in the experimental group.

POSTSUBICULUM

Additional evidence for the HD signal's role in navigation is provided by studies of navigation in animals with PoS lesions. Both NMDA and electrolytic PoS lesions impaired radial arm and water maze performance, but did not impair performance on a nonspatial cued version of the water maze or on a conditioned food aversion task (Taube et al., 1992). PoS lesions also impaired spatial alternation on a T-maze when the second trial was delayed (Bett et al., 2012). However, this study also showed that PoS lesions did not impair homing on a food-hoarding task (but see Valerio et al., 2011 for an opposite account). The intact homing after PoS lesions is particularly interesting, given the Frohardt et al. (2006) report (mentioned above) of impaired homing after DTN or ADN lesions. Together, these results suggest that HD signal generation is necessary for homing, but this function does not depend on the transfer of HD information out of PoS. Another possibility is that the direct projection from ADN to retrosplenial cortex (van Groen and Wyss, 1990a, 2003), which may include the HD signal, is sufficient to support path integration, given that the retrosplenial cortex contains HD cells (Chen et al., 1994; Cho and Sharp, 2001) and is necessary for path integration (Cooper and Mizumori, 1999; Whishaw et al., 2001).

In addition to its role in navigation, the PoS also contributes to functions other than the HD signal. A recent study found that blockade of PoS kainate and AMPA receptors with CNQX disrupted the stability of hippocampal place cells, whereas AMPA/kainate receptor blockade or NMDA receptor blockade with D-AP5 impairs object-location memory (Bett et al., 2013). PoS lesions also impaired the acquisition of contextual fear, and impaired both the acquisition and expression of auditory conditioned fear (Robinson and Bucci, 2012). Thus, it remains unclear whether the predominant PoS contribution to navigation involves the transfer of the HD signal to cortical structures or the transfer of object-location information to the HD and other spatial signals. We can conclude, however, that the HD signal is necessary for navigation, as HD signal disruption at any point within the ascending HD circuit disrupts navigation.

HD SIGNAL INVOLVEMENT IN NAVIGATION – ELECTROPHYSIOLOGY AND BEHAVIOR

The importance of the HD signal for navigation is indicated by lesion studies, but its exact contribution to navigation is not well understood at the present time. One possibility is that the HD signal serves as a reference (or compass) by which animals navigate. If true, the HD signal would remain constant within a given environment and navigation would change relative to the HD signal (and thus, the environment) based on reward contingencies. A study of HD cell activity during navigation on parallel T-mazes supports this idea (Dudchenko and Zinyuk, 2005). In T-mazes located in adjacent rooms, an HD cell's preferred firing direction remained constant when the mazes were parallel, but reoriented to the second maze when it was rotated 90° relative to the first maze, suggesting that the HD signal was controlled by the maze instead of by distal room cues. A more recent study found that both HD and grid cells in the entorhinal cortex were controlled by distal cues to a greater extent than by cues within the T-maze if the maze was navigated recently, but to a lesser extent if the maze was navigated at an earlier time (Gupta et al., 2014). Dudchenko and Zinyuk (2005) also provided evidence for HD signal involvement in path integration-based navigation. In an apparatus consisting of four interconnected chambers, the preferred firing direction remapped if the animal was passively transported between arenas, but remained stable if the animal walked between arenas. Similar results were found with the dual-chamber apparatus and a two-room maze, where passive transport from familiar to novel arenas caused HD signal remapping, but active locomotion maintained HD signal stability between arenas (Taube and Burton, 1995; Stackman et al., 2003; Yoder et al., 2011a). However, this compass-like representation across arenas does accumulate error over time and distance traveled in path integration tasks. For example, instead of remaining constant, the HD signal was updated relative to the environment when a previous journey contained errors (Valerio and Taube, 2012). Blindfolded rats were trained to perform a food-carrying task where the animal foraged for food and then relied on path integration during the outbound journey in order to calculate a direct return path back to the start box in order to consume the food. After training, rats

were implanted with electrodes aimed at HD cells in the ADN. As predicted, there was a correlation between the amount of error in the HD signal (comparing the HD cell's preferred direction in the refuge to its value at the onset of the return trip) and the amount of error in the rat's behavioral trajectory. When the rat made an error in its return path, the cell's preferred direction was usually "reset" to its initial value in the refuge. However, on some occasions – particularly when large errors occurred, the HD signal "remapped," with the cell's new preferred firing direction corresponding to the angular error experienced on the rat's return path to the refuge. In other words, rather than correcting the error upon return to the refuge and "resetting" its preferred direction based on the known reference cues within the refuge, the cell adopted a new preferred direction based on how it fired during the rat's erroneous return path to the refuge. This finding suggests that, although the HD can be controlled by path integration, the reward system can override this control in order to update the signal when necessary. This study therefore provides important insight into the relation between the HD signal and behavior, although it is presently unknown whether similar updating occurs during landmark navigation, which usually dominates the control of spatial signals. Future studies are therefore important to further elucidate the role of the HD signal in navigation, as well as the nature of the information it carries.

The vestibular system also appears to play an important role in the formation of a cognitive map. One study showed that when rats were inverted (upside-down), they had difficulty finding an escape hole from four different entry points, but can learn to solve the task when released from one or two entry points (Valerio et al., 2010). This spatial impairment could have resulted from the disrupted HD signal that occurs when rats navigate in an inverted position, as discussed above. To test this, a subsequent study monitored HD cell activity in the two entry-point version of the inverted task and when the rats were released from a novel start point (Gibson et al., 2013). The authors found that, despite the absence of direction-specific firing in HD cells, rats could successfully navigate to the escape hole when released from one of two familiar locations by using a habit-associated directional strategy. Moreover, in the continued absence of normal HD cell activity, inverted rats failed to find the escape hole when they started from a novel release point. These results suggest that the HD signal is critical for accurate navigation in situations that require a flexible representation of space, such as when using a cognitive mapping strategy, but not in situations that utilize habit-like associative spatial learning. Further, it was the direct result of being inverted and possibly experiencing an unfamiliar otolith signal that led to the disruption of direction-specific firing in HD cells.

CONCLUSION

Overall, we currently have considerable evidence that the vestibular system contributes to spatial signals and navigation. The semicircular canals are necessary for HD signal generation, whereas the otolith organs support HD signal stability. Given the vestibular involvement in HD signal generation, the HD signal appears to convey at least a portion of the vestibular contribution to spatial functions. Our understanding of this contribution continues to develop as new approaches become available for the investigation of the roles of the semicircular canals and otolith organs in spatial cognition.

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