Central vestibular networking for sensorimotor control, cognition, and emotion

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Purpose of review
The aim of this study was to illuminate the extent of the bilateral central vestibular network from brainstem and cerebellum to subcortical and cortical areas and its interrelation to higher cortical functions such as spatial cognition and anxiety.

Recent findings
The conventional view that the main function of the vestibular system is the perception of self-motion and body orientation in space and the sensorimotor control of gaze and posture had to be developed further by a hierarchical organisation with bottom-up and top-down interconnections. Even the vestibulo-ocular and vestibulo-spinal reflexes are modified by perceptual cortical processes, assigned to higher vestibulo-cortical functions. A first comparative fMRI meta-analysis of vestibular stimulation and fear-conditioning studies in healthy participants disclosed widely distributed clusters of concordance, including the prefrontal cortex, anterior insula, temporal and inferior parietal lobe, thalamus, brainstem and cerebellum. In contrast, the cortical vestibular core region around the posterior insula was activated during vestibular stimulation but deactivated during fear conditioning. In recent years, there has been increasing evidence from studies in animals and humans that the central vestibular system has numerous connections related to spatial sensorimotor performance, memory, and emotion. The clinical implication of the complex interaction within various networks makes it difficult to assign some higher multisensory disorders to one particular modality, for example in spatial hemineglect or room-tilt illusion.

Summary
Our understanding of higher cortical vestibular functions is still in its infancy. Different brain imaging techniques in animals and humans are one of the most promising methodological approaches for further structural and functional decoding of the vestibular and other intimately interconnected networks. The multisensory networking including cognition and emotion determines human behaviour in space.

Keywords
anxiety, cognition, cortical networks, sensorimotor, vestibular

INTRODUCTION

The conventional view of the major functions of the vestibular system is of its contribution to the perception of self-motion and body orientation in the 3D environment and the sensorimotor control of gaze and posture. This simplification can be broadened by a concept of a hierarchical organisation subdivided into three sensorimotor anatomical and functional levels that are interconnected in both directions, bottom-up and top-down. The resulting sensorimotor and cognitive achievements within this vestibular network can be assigned topographically from caudal brainstem to cortex structures [1,2]: reflexive control of gaze, head, and body position in three spatial planes at brainstem-cerebellar level; perception of self-motion and integration of reflexive and voluntary movements and balance at subcortical/cortical level; and higher vestibular cognitive functions such as spatial memory and navigation and behavioural sensorimotor control mainly at cortical level.

Only in recent years have new higher cortical vestibular functions been recognized – beyond rare cortical vertigo syndromes [3,4] – with integration of

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KEY POINTS

- The most clinically relevant, recent understanding of vestibular function is based on the extensive distribution of the vestibular network interactively linked with multisensorimotor systems, perception, higher cognition and emotional networks for human behaviour in 3D space.
- The bilateral central vestibular network extends from the vestibular nuclei in the caudal pontomedullary brainstem via the midbrain and thalamus to multiple cortex areas with the core region in the insular-opercular cortex. The network also includes the ventrolateral prefrontal cortex, the parietal lobe, cingulum and cerebellar vermis and hemispheres.
- The anxiety network is similarly complex and distributed from the parabrachial nuclei in the pontine brainstem up to the prefrontal cortex. There are multiple clusters of vestibular and anxiety concordance for activation, in particular in the anterior insula and ventrolateral prefrontal cortex. In contrast, in the posterior insula activations were found during vestibular stimulation but deactivations during fear conditioning, possibly a mechanism to downregulate the fear network in acute vestibular disorders.
- Experimental postural threats such as expected body perturbations or exposure to visual heights elicit anxious control of postural stability with leaning forward, co-contraction of antigravity muscles and a general stiffening of the whole body including the neck and ocular motor apparatus. This reflects a modification of vestibulo-ocular and vestibulo-spinal reflexes by cognition.
- Studies in animals and humans have shown that the central vestibular system has numerous connections with brain areas related to memory such as vestibular thalamic head direction cells, hippocampal place cells and entorhinal grid cells.
- Bilateral peripheral vestibulopathy not only impairs spatial memory and navigation but also mental rotation, sensory response inhibition, auditory and visual working memory as well as cognitive-motor interference in dual tasking, for example, when balancing on a postural platform.

nonvestibular senses and emotional processes. This review will focus on new insights into the complex central vestibular network that extends from the lower brainstem and cerebellum to multiple cortical areas [5,6] and its overlap with other sensory and emotional systems of a similarly complex distribution such as that of the anxiety network. The presentation of recent discoveries will be grouped into sensorimotor control, anxiety/emotion and cognition. The selection of central vestibular system analysis is based methodically on imaging studies, neurophysiological, psychophysical and clinical data.

SENSORIMOTOR CONTROL

The vestibulo-ocular and vestibulo-spinal reflexes and their cortical modifications

The short-latency response of the vestibulo-ocular reflex (VOR), as based on a di and tri-synaptic neuronal arc, is embedded into a distributed bilateral network of neurons with the vestibular nuclei as the caudal central structure [7]. The peripheral vestibular input converges at vestibular nuclei level with that from other sensory modalities, in particular visual and somatosensory input. Ascending multisensory vestibular pathways branch to vestibular cortex areas for perception, while descending pathways convey vestibular input to the spinal cord for control of head and body position in space. Consequently, brainstem lesions that disturb VOR function not only cause nystagmus but also postural instability, vertigo and spatial disorientation [7]. Vestibular nucleus neurons integrate inputs from a variety of sensory sources in that vestibular reflexes are shaped in accordance with ongoing movements and behaviour [8]. With respect to vestibulospinal signals, two pathways mediate vestibular information to limb motoneurons via the lateral vestibulospinal tract and reticulospinal projections, both of which are influenced by supratentorial regions [9]. This is in line with recent findings that, for example, the amplitude of click-induced cervical vestibular myogenic-evoked potentials was enhanced during visually elicited apparent self-rotation, which correlated with the strength of subjective roll vection [10]. Thus, even vestibulospinal reflexes at brainstem level are modified by perceptual cortical processes, assigned to higher vestibulo-cortical functions.

This modification by cortical processes can also be seen in conditions in which anxiety, fear and threat play an important role in affecting sensorimotor control of gaze, posture and locomotion [11,12]. Experimental postural threats, such as the expectation of receiving a body pertubation, elicited complex modifications to standing balance characterized by an increased sample entropy, leaning forward and increasing the amplitude and frequency of the centre of body pressure displacements in healthy participants [13]. In functional dizziness patients (phobic postural vertigo), pathological eye-head coordination correlated with a higher level of discomfort and anxiety about falling and gaze control exhibited shorter durations of visual fixation as compared to healthy controls [14]. Further, self-adjusted speed of locomotion was significantly

slower. In parallel, neurophysiological analysis of stance and gait in patients with visual height intolerance and acrophobia also revealed an anxious control of postural stability, which initiated a co-contraction of antigravity muscles that caused a general stiffening of the whole body including the neck and ocular motor apparatus [15,16▪]. When experimentally exposed to heights, visual exploration was preferably reduced to fixation of the horizon and gait alterations were characterized by a cautious slow walking mode with reduced stride length and increased double support phases (Fig. 1). Hence, anxiety about falling down or falling off is the critical factor in both phobic postural vertigo and acrophobia. Postural changes during height exposure are linked to an increased self-awareness of body sway [17].

Anxiety and depression not only influence eye, head, and body movements in individuals with normal vestibular test results, but also affect patients with different types of vestibular syndromes, whether they are acute, episodic or chronic. In anxious patients, the degree of handicap and the probability of increased vertigo was 4.65 times that of nonanxious patients and the probability of increased vertigo in depressed patients was 3.49 times that of nondepressed patients [18]. There is some evidence that the vestibular system and the cerebellum – by means of reciprocal interconnections within a multilocal anxiety system – influence both cognition and emotional regulation in animals and humans [19,20]. Indeed, almost half of patients with vertigo and dizziness of a large, unselected sample, referred to a specialised, interdisciplinary centre for vertigo and dizziness, suffered from a psychiatric comorbidity [21]. In 48.8% of such patients, psychometric testing led to the diagnosis of a current psychiatric disorder, most frequently anxiety/phobic, somatoform, and affective disorders. In particular, patients who suffered from episodic vertigo, namely vestibular paroxysmia, vestibular migraine or Meniere's disease, had the highest prevalence of psychiatric disorders [21,22]. One hypothesis may be that patients perceive the onset and intensity of vertigo/dizziness attacks as uncontrollable, which triggers anxiety and panic-related cognition and sometimes leads to the development of avoidance behaviour [23,24]. Previous studies had also suggested a link between anxiety and balance disorders because migraine and anxiety were often found in combination. More generally, neuroanatomical connections between the vestibular system and neuronal pathways were hypothesized to possibly be involved in anxiety/phobic conditioning, modulated by monoaminergic and noradrenergic influences [25,26].

In contrast, patients with a loss of peripheral vestibular input by unilateral or bilateral vestibulopathy (BVP) – as distinct from other vestibular disorders – showed lower rates of associated anxiety about falling [27] or susceptibility to fear of heights despite their postural instability and higher risk of falling [28]. The above-described interrelations raised the question whether an intact vestibular function is required to develop vertigo related anxiety [29].

How is the sensory vestibular system connected to sensorimotor control to allow for quick responses in a threatening situation? Lesion-network mapping suggests a functional segregation of upstream vestibular projections via the thalamus with an ipsilateral pathway connecting directly to the multisensory vestibular cortex in the posterior insular-opercular region and a contralateral pathway targeting sensorimotor cortical areas [30▪]. This functional organization allows stable perceptual representation and flexible adaptation of body control to sudden changes in the environment.

To examine the connections between both systems, only recently, the structural and functional interaction between the branched and widely distributed vestibular and anxiety networks were studied by fMRI.

ANXIETY AND EMOTION

Structural and functional interaction of the vestibular and the anxiety networks

A meta-analysis of earlier fMRI studies applying vestibular stimulation and fear conditioning [31] was conducted in healthy participants to test a potential overlap of vestibular and fear systems with regard to their brain imaging representation maps [32▪▪]. Common clusters of concordance of vestibular stimulation and fear conditioning were also found bilaterally within the widely distributed network. Both networks extend from the caudal pontine brainstem, the vestibular nuclei for the vestibular system, and the parabrachial nuclei for the fear/anxiety system, to multiple cortex areas (anterior insula cortex, ventrolateral prefrontal cortex and the right temporal pole, bilaterally in the adjacent ventrolateral prefrontal cortex, cingulate gyrus, secondary somatosensory cortex, superior temporal and intraparietal lobe, supplementary motor area and premotor cortex, as well as subcortical areas, such as the bilateral thalamus, mesencephalic brainstem, including the collicular complex, pons, cerebellar vermis and bilateral cerebellar hemispheres) (Fig. 2). Interestingly, peak areas of high concordance for activations during vestibular stimulation but deactivations during fear conditioning were centred on the

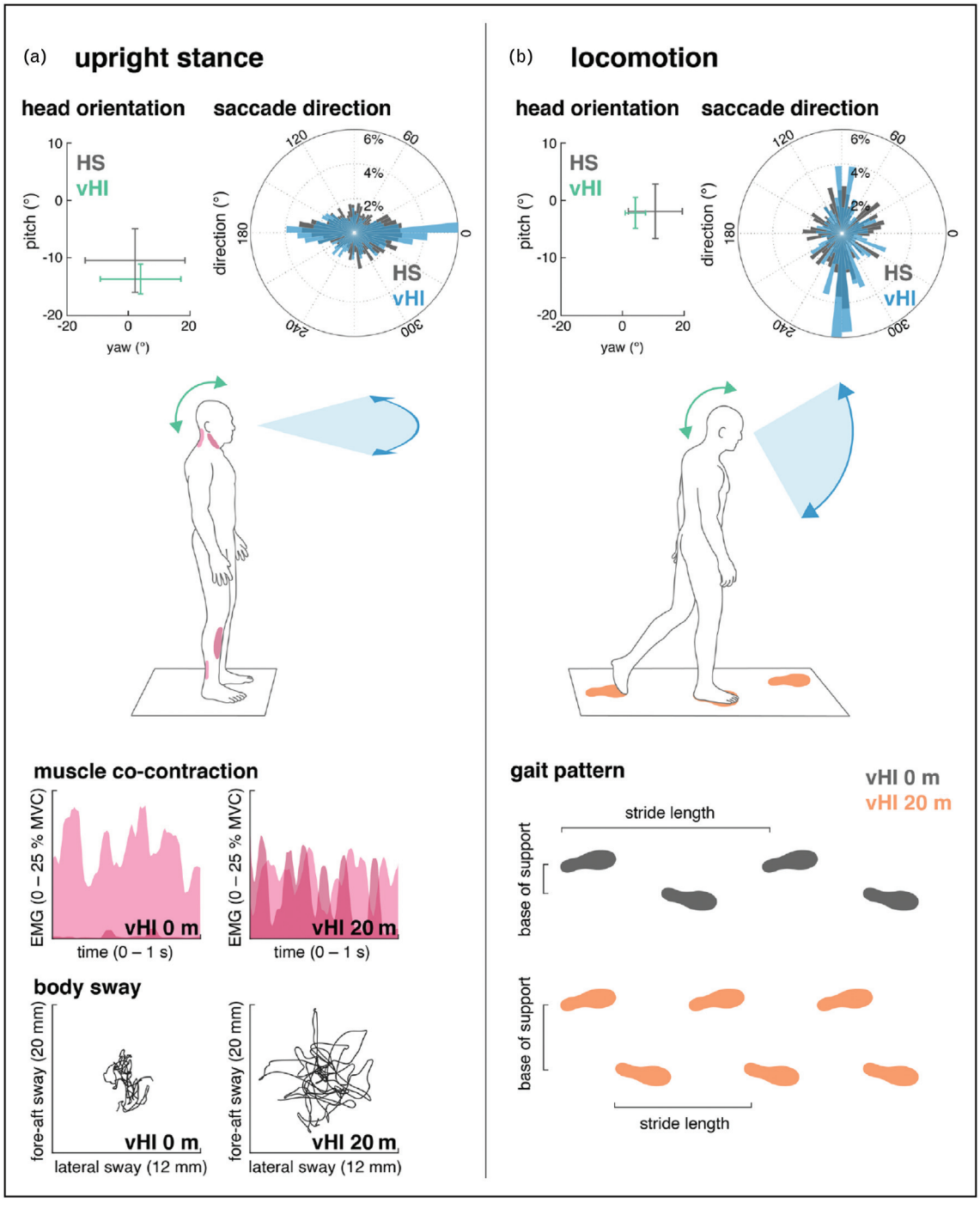

FIGURE 1. Overview of height-induced alterations of visual exploration, postural and locomotion control in individuals with visual height intolerance (vHI) and healthy insusceptible individuals (HS) while being exposed to heights on an emergency balcony 20m above ground. (a) Behavioural alterations during quiet upright stance. (b) Behavioural alterations during locomotion. Top: group means and interquartile ranges of head orientation and histograms of the direction of corresponding saccadic eye movements. During both standing and walking, vHI show considerably reduced head movements. Saccadic eye movements during stance in vHI are preferably directed along the horizontal plane. In contrast, during locomotion, they perform saccades primarily along the vertical plane. Bottom: during height exposure, postural control in vHI is characterized by increased co-contraction of antigravity muscles and increased body sway amplitudes. Locomotion is characterized by a slow and cautious mode of walking, with a reduced stride length and a broadened base of support (from [16▪]).

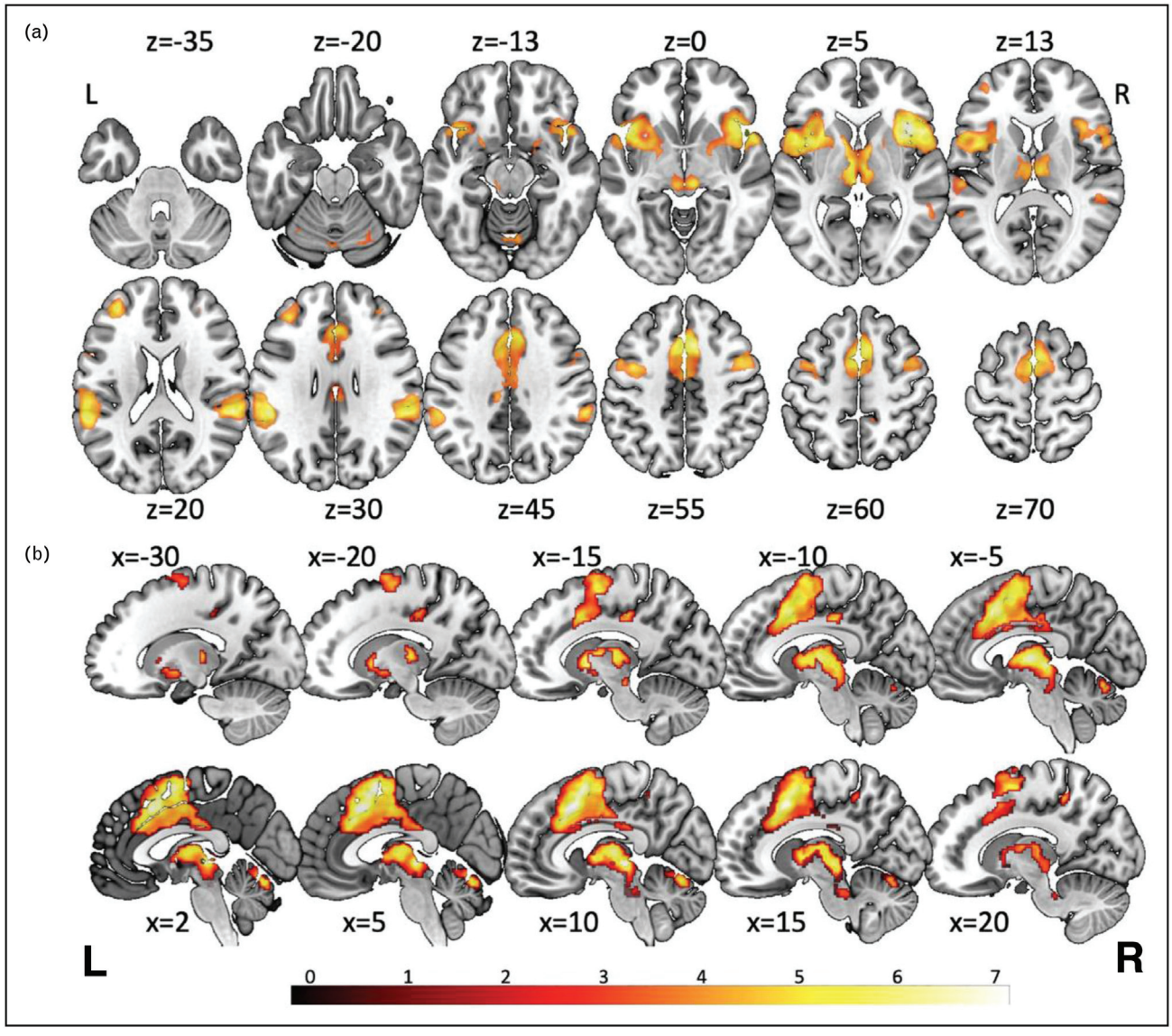

FIGURE 2. Brain regions showing significant high concordance for vestibular stimulation (analysis presented in [32▪▪]) and fear conditioning (meta-analysis published in [31]). Color bar provides *z* value coding. Z-position plotted above each axial/transversal slice. (a) For axial slice overlay of the conjunction analysis between the two conditions, activations were significant for the anterior insula, frontal lobe areas, subcortical structures temporal areas (Heschl gyrus; superior and middle temporal gyrus), and parietal areas (S2, IPL). (b) The cluster of concordance around the brainstem showed activation in the thalamus, periaqueductal gray, nucleus rubber, dorsal midbrain, vermis and posterior cerebellar hemispheres. Overall, all areas of high concordance detected for vestibular activation in the brainstem, thalamus and cerebellum were also active during fear conditioning (from [32▪▪]).

posterior insula and S2 bilaterally [32▪▪,64] (Fig. 3). This structural overlap of both networks allows some functional interpretations: first, the amygdala, superior colliculi, and antero-medial thalamus might represent a release of preprogramed sensorimotor patterns of approach or avoidance, and second, the activation (vestibular system) and deactivation (fear system) of the bilateral posterior insula are compatible with the view that downregulation of the fear network by acute vestibular disorders or unfamiliar vestibular stimulation makes unpleasant perceived body accelerations less distressing [32▪▪]. The latter interpretation is based on the earlier developed fundamental concept of a reciprocal inhibitory interaction between sensory systems: experimental activations of the vestibular cortical network were associated with concurrent deactivations of the visual and somatosensory cortex areas (for review: [2]).

Originally, this pattern of reciprocal activations and deactivations was found during visually

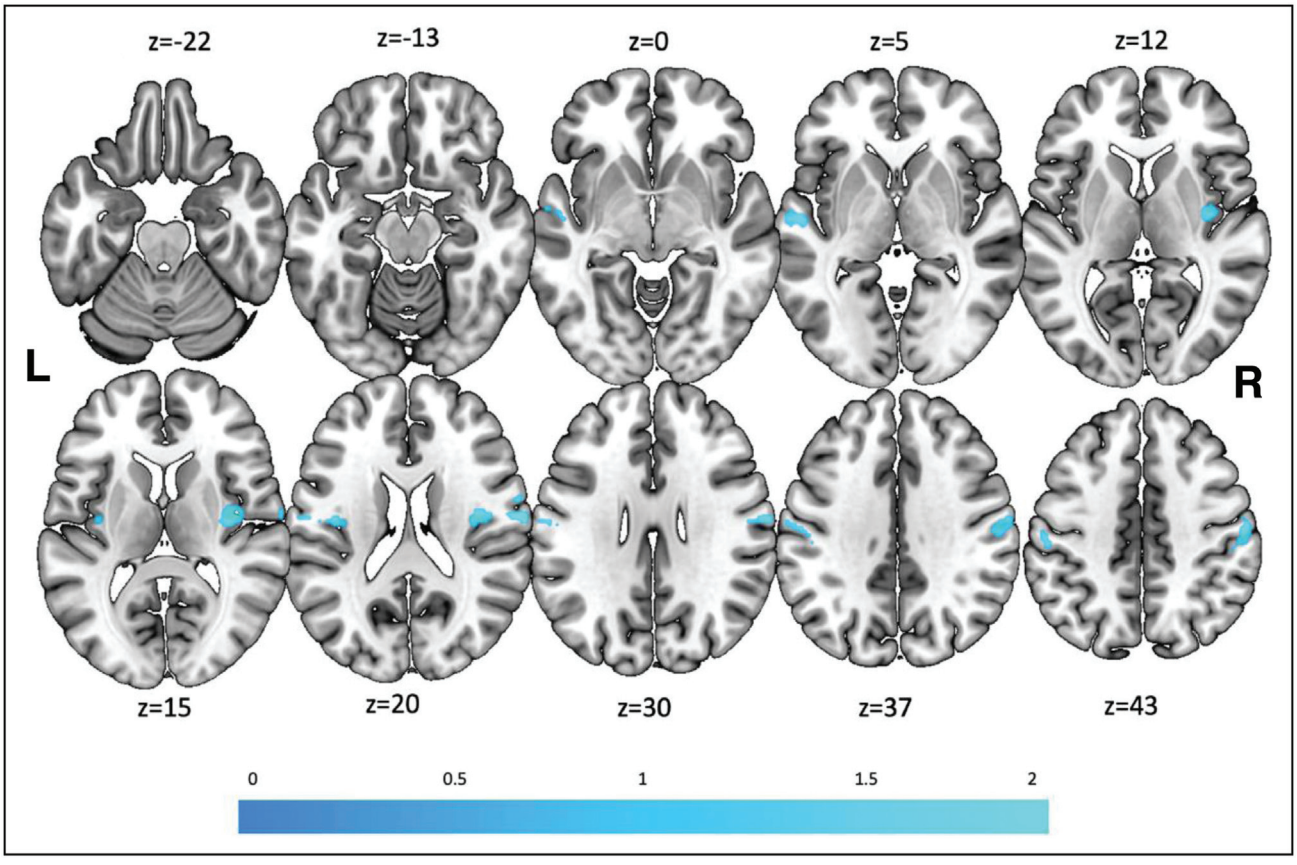

FIGURE 3. Regions of concordance for activation during vestibular stimulation and deactivation during fear conditioning: right postcentral gyrus, bilateral insula (predominantly anterior long insular gyrus, i.e., first long insular gyrus according to [64]), S2 (predominantly OP1 and OP3), and left superior temporal gyrus (color bar provides z value coding). Axial/transversal slice position is plotted as z-coordinates for the MNI-system [32▪▪].

induced self-motion perception, for example, activations of occipital and parietal visual areas were associated with deactivations of the multisensory vestibular cortex [33]. The functional interpretation was that during motion perception the dominant sensorial weight might be shifted from one modality to the other, thereby resolving conflicts of a sensory mismatch. Later, such interactions were also described for other sensory modalities, for example, the somatosensory and nociceptive, the nociceptive and the vestibular, the tactile sensory and the visual, and the visual and auditory systems [34–36] as well as smell and sleep [37].

The assumption of a reciprocal inhibitory interaction between the vestibular and anxiety systems in the recent study [32▪▪] is in agreement with the clinical observation that patients with bilateral vestibular loss [27] and deficits in central vestibular structures (e.g. cerebellar ataxia, downbeat nystagmus) [38] suffer from less vertigo-related anxiety, although they complain of imbalance and have a higher handicap of falling. This mechanism possibly has the goal to weaken distressing anxiety and vegetative effects of unusual excessive vestibular stimulations or acute vertigo syndromes [29]. This is in line with the clinical finding that psychiatric comorbidity and vertigo-related anxiety are maximal with vestibular excitation and minimal with loss of vestibular function [29].

Remarkably, dogs exhibited a similar cortical distribution of the anxiety networks as compared to humans [39]. The prevalence of anxiety disorders in dogs is high. Anxious dogs showed significantly decreased clustering, decreased global efficiency, increased small-worldness of the network structure, as well as increased 'betweenness centrality' in the right insular cortex. The authors explain that this increased 'betweenness centrality' for the right insula within the brain networks indicates a more central and influential role for this brain area in anxious dogs [39,40].

Altered functional connectivity networks were also found in patients with functional dizziness related to anxiety. In a multimodal MRI study, 44 patients with functional phobic postural vertigo showed higher functional connectivity compared to healthy participants between the prefrontal cortex (fpPFC) and thalamus, anterior insula,

parahippocampus, anterior cingulum, amygdala and posterior medial frontal gyrus [11]. Further, a volume reduction of gray matter was seen in the cerebellum and a concurrent volume increase in the bilateral thalamus and motor cortex [11]. This was explained by a reduced automated sensorimotor control (cerebellum) on the one hand and an enhanced voluntary sensorimotor control (cortex) on the other. Areas with the enhanced connectivity belong to the wider network of emotions, anxiety and depression, also presenting with a stronger connectivity in depression and anxiety disorders [41]. This is in accordance with the finding that the Beck-Depression-Inventory was positively correlated with gray matter volume increases of several prefrontal cortex areas and the precentral gyrus but negatively correlated (volume decrease) with cerebellar areas and the middle occipital gyrus [11,42]. Moreover, cortical thickness revealed greater values in healthy controls compared to the patients for the ventromedial prefrontal cortex, the insular sulcus and the lingual gyrus in the left hemisphere, and a region bordering the anterior cingulate gyrus and the cuneus in the right hemisphere [11]. Accordingly, an altered functional brain connectivity between the cerebellum and the thalamus was also described in other imaging studies in patients with persistent postural perceptual dizziness (PPPD) [43–46]. A dysfunction of precuneus and cuneus in the resting state with altered intra- and inter-network functional connectivity was interpreted as a potential cause of an abnormal integration of visual and vestibular information and abnormalities in external environment monitoring [45]. Functional dizziness could arise from shifts in interactions among visuo-vestibular, sensorimotor, and emotional networks that overweigh visual over vestibular inputs and increase the effects of anxiety-related mechanisms on locomotor control and spatial orientation [46].

Moreover, using intracranial recordings in neurosurgical patients, neuronal activity in the multilocal entorhinal cortex, that is, the medial temporal lobe, revealed a grid-like pattern across a 2D space when performing an emotional memory task [47]. This could indicate that grid cells processing vestibular information might also be involved in emotional cognition by forming a 2D emotion space and thus could have a more general role for different behavioural functions. In another study with presurgical intracranial stereotactic recordings, a retrospective analysis revealed in some patients pleasant rather than unpleasant emotions [48▪]. Here, the right hemisphere with the dorsal anterior insula and amygdala played a preponderant role. Connectivity studies have also revealed possible hints to psychiatric disorders, for example, in autism spectrum disorders as a result of a reduced deactivation of the prefrontal cortex mPFC during global task processing [49▪].

COGNITION

Over the last decades, especially in the last 3 years, there has been increasing evidence from studies in animals [50–52] and humans [53–56] that the central vestibular system has numerous connections with brain areas related to memory, such as thalamic head direction cells, hippocampal place cells, and entorhinal grid cells [57▪]. Disorders of 'higher' vestibular functions involve more than one sensory modality and cognitive domain and include, for example, hemispatial neglect and room-tilt illusion with a less favourable course if elicited by lesions in the vestibular-dominant right hemisphere [58]. Higher vestibular disorders not only occur with central vestibular lesions [59] but also with peripheral vestibular deficits such as in patients with BVP [60]. BVP not only affects visuospatial abilities but could also decrease processing speed, memory, and executive functions [61]. A prospective case-controlled study on cognitive and motor performance and cognitive-motor interference in patients with BVP confirmed deficits in visuospatial memory and further disclosed poorer auditory and visual working memory [62▪▪]. With dual tasking, for example, balancing on a force platform covered with a foam pad, cognitive impairment was enhanced compared to the tests performed while seated. In real space navigation tasks, vestibular loss turned out to particularly affect the neural representation of 'novel' spatial information; the deficits correlated with the degree of BVP [53]. In patients with unilateral vestibular loss (UVL), deficits seem to be more heterogeneous, milder, more circumscribed, and transient [57▪], while the affected ear plays an important role [63]. For instance, only a right-sided dysfunction in UVL patients reduced the odds of adopting an allocentric spatial strategy in a virtual reality reverse T-maze [55] and showed significant decreased scores in visuospatial perception and memory in the acute phase [63]. More variable effects on cognition in UVL can be due to several factors including different degrees of vestibular deficits, different time courses and aetiologies as well as concurrent hearing disturbance, psychiatric comorbidity, and altered or enhanced attention.

CONCLUSION

The most clinically relevant, recent understanding of vestibular function is based on the extensive

distribution of the vestibular network interactively linked with multisensorimotor systems, perception, higher cognition and emotional networks for human behaviour in 3D space. This comprehensive recognition helps to decode the contribution of the vestibular system not only to equilibrium, locomotion and navigation, but also to task-dependent behaviour adapted to life.

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Conflicts of interest

The authors have no conflicts of interest.

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