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Animal studies linking the vestibular system and memory: Aotearoa/New Zealand's contribution

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ABSTRACT

Animal studies of the mammalian vestibular system began at the University of Otago in 1987. From approximately 2000, these studies focused on the effects of vestibular lesions and stimulation, on spatial memory and the hippocampus. Our research has shown that, as well as the deficits in the vestibulo-ocular and vestibulo-spinal reflexes that occur following vestibular dysfunction, vestibular loss may also cause cognitive disorders, especially spatial memory deficits, some of which are related to the contribution of ascending vestibular pathways to the function of the limbic system and neocortex in regulating spatial orientation. In addition to behavioural demonstrations of spatial memory deficits, we have demonstrated that vestibular loss is associated with a variety of dysfunctional changes in the hippocampus, which may be responsible for the spatial memory deficits. These memory deficits are unlikely to be due to hearing loss, problems with motor control, oscillopsia or anxiety and depression. These animal studies have raised awareness of cognitive deficits associated with vestibular disorders and contributed to their recognition and treatment.

Abbreviations: UVL: unilateral vestibular lesion; BVL: bilateral vestibular lesion; VNC: vestibular nucleus complex; DG: dentate gyrus; VOR: vestibulo-ocular reflex; VSR: vestibulo-spinal reflex

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Introduction

Loss of vestibular function, caused by a dysfunction of the balance organs in the inner ear (the 'vestibular system'), is associated with visual symptoms such as blurred vision ('oscillopsia', caused by the loss of the vestibulo-ocular reflexes (VORs)) and difficulty standing and walking ('ataxia', caused by the failure of the vestibulo-spinal reflexes (VSRs)) (see Vidal et al. 2014 for a review). The VORs are generated by a change in head velocity (i.e. an 'acceleration') and compensate for unintentional head movement, by generating eye movement that is equal and opposite, thus maintaining the stability of visual images

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on the retina and preventing retinal slip. The VSRs, also activated by head acceleration, generate changes in posture to help maintain balance (see Vidal et al. 2014 for a review). However, an additional function of the vestibular system involves the transmission of head movement information to the limbic system and neocortical areas of the brain, in order to produce a conscious sense of head movement and a memory of it. This aspect of vestibular function has, historically, received much less attention than the vestibular reflexes; however, the vestibular system is now recognised to make important contributions to cognitive function, particularly spatial memory, and it has been proposed that vestibular dysfunction may contribute to the risk of dementia (see Agrawal et al. 2020 for a review). Information transmitted from the peripheral vestibular endorgans appears to be necessary for the brain's internal representation of the relationship between the self and the spatial world, integrating vestibular information with visual, auditory, proprioceptive and somatosensory information (see Moser et al. 2017; Jeffery 2024 for reviews). Without vestibular information, the internal representation becomes degraded and cognitive performance deteriorates.

Mechanistic animal research on the mammalian vestibular system began in the 1980s in Aotearoa/New Zealand when two of us (Paul Smith and Cynthia Darlington) moved here from the University of Sydney. This research was first conducted in the Dept. of Psychology at the University of Otago in Dunedin (1987–1995), and then in the Dept. of Pharmacology at the same University (1995-present). Initially, these studies using guinea pigs as the experimental subjects, investigated the process of recovery from peripheral vestibular dysfunction ('vestibular compensation') using a combination of behavioural and electrophysiological (*in vitro* brain slice recording) methods. By the late 1990s, the focus of the research had turned to the effects of lesions of the vestibular system on the hippocampus, and guinea pigs had been replaced by rats. It was at this stage that Yiwen Zheng joined the group as a Post-Doctoral Fellow in 1998. This review will focus on the history of this research at the University of Otago on the association between the vestibular system, memory and the hippocampus, against the context of research outside New Zealand, and attempt to show how our research has contributed to the understanding of the connection between vestibular dysfunction and memory (see Smith et al. 2015 for a detailed review).

In the USA, vestibular disorders are estimated to occur in more than 35% of adults aged 40 or older, and increase to almost 50% from 60 to 69 years (Agrawal et al. 2009). It is estimated that 3.9 million patients visited a Hospital Emergency Department in the USA in 2011 for dizziness or vertigo, and 25.7% of visits were associated with vestibular causes, costing U$757 million (Saber Tehrani et al. 2013). Agrawal et al. (2009) reported that patients with vestibular disorders had a 12-fold increase in the risk of falling, the most common cause of death in the elderly. Vestibular disorders therefore represent a major and increasing burden on the healthcare system.

Vestibular lesions and memory in animals

The concept that the vestibular system in the inner ear might contribute to spatial navigation and spatial memory is not new: in fact, it was first suggested in the 1960s by physiologists such as Beritoff (1965). Early studies of spatial navigation in animals showed that 'idiothetic' cues (non-visual, internal ones, for example, vestibular and proprioceptive

stimuli), in addition to 'allocentric' cues (external ones, such as visual information), were used to remember navigation routes through space (Beritoff 1965; Potegal et al. 1977; Etienne 1980; Mittelstaedt and Mittelstaedt 1980). Decades later, it was reported that vestibular information is sent to the hippocampus, a critical brain region for spatial memory, and integrated with other sensory information (Wiener and Berthoz 1993; Berthoz 1996; McNaughton et al. 1996; Etienne and Jeffery 2004). Eventually it was reported that that 'place cells' in the hippocampus, which respond to different places in the environment, were regulated by vestibular information (Gavrilov et al. 1995; Wiener et al. 1995). This finding was consistent with behavioural studies demonstrating that vestibular loss caused spatial memory deficits (e.g. Baek et al. 2010; Russell et al. 2003a; Stackman and Herbert 2002; Wallace et al. 2002; Zheng et al. 2006, 2009).

The first studies were open to some criticisms. Many studies were conducted in light, Therefore, the spatial memory deficits could have been caused by oscillopsia, due to the VOR deficits, or ataxia, caused by the VSR deficits. Some compensation occurs over time (i.e. 'vestibular compensation'), but the reflex deficits never completely resolve (Smith and Curthoys 1989; Curthoys and Halmagyi 1995). Furthermore, some studies used chemical ototoxic injections into the tympanic membrane (ear drum) in order to lesion the vestibular system, and it was difficult to discount the possibility that some of the behavioural effects were due to cochlear damage. This was an important consideration because in the last 10 years it has been shown that hearing loss can cause spatial memory impairment as well (see Smith 2022 for a review). Beginning in the early 2000s, our research group began conducting studies that controlled for some of these issues, by conducting spatial memory tests in darkness as well as light, and at long time intervals following the peripheral vestibular lesions, when at least some degree of compensation for the reflexive deficits had occurred. We also employed partial auditory controls by surgically removing the tympanic membrane in control rats. Our initial studies were conducted using the foraging task developed by Ian Whishaw, which he and his colleagues used to show that bilateral chemical vestibular lesions in rats caused spatial memory deficits (Wallace et al. 2002; Figure 1). Yiwen Zheng underwent specialist training in the laboratory of John Aggleton at Cardiff University, who had used the foraging task extensively, and learned how to meticulously conduct these experiments; she became chiefly responsible for them over the next decade. Using Whishaw's foraging

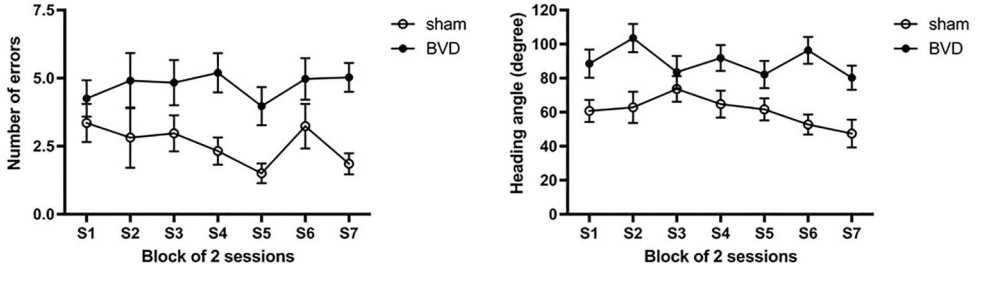

Figure 1. Number of errors **A** and heading angles **B** for the sham and BVD rats during the dark sessions of a foraging task. Data reflect a block of two sessions and are presented as mean ± SEM. Reproduced with permission from Zheng et al. (2009).

task, the role of vestibular information in the development of spatial memory could be precisely investigated by comparing the animal's performance with and without visual cues (i.e. performance in light *versus* in darkness; Figure 1).

We focused on using 3–6 month delays after the vestibular lesion, when some reflexive recovery had occurred and the animals were not prevented from performing in memory tasks by motor deficits (Baek et al. 2010; Zheng et al. 2006, 2007, 2009, 2009b, 2012a). In one study we used a delay of 14 months after bilateral vestibular lesions (BVL), and demonstrated that rats exhibited worse memory impairment in a foraging task compared to 5 months post-op. In most of our studies, we have used unilateral or bilateral peripheral vestibular surgical lesions, in which we visualised the vestibular inner ear components (the anterior, horizontal and posterior semi-circular canals, the utricle and saccule) using an ENT microscope, drilled into them using a fine dental drill, and aspirating their contents which include the sensory hair cells (Baek et al. 2010; Zheng et al. 2006, 2007, 2009, 2009b, 2012b). This method, although much harder technically than chemical injections through the tympanic membrane, is more selective for the vestibular system. In addition, as a surgical control, we included rats that did not have a vestibular lesion but had the tympanic membrane removed in order to cause partial deafness (some sound vibrations will still reach the cochlea). By doing this, we could compare the effects of hearing loss with vestibular loss and whatever incidental damage to the cochlea we might have caused with the vestibular surgery.

Some more recent studies have examined the specific role of the semi-circular canals and the otoliths, in spatial memory. Yoder et al. (2015) employed '*tilted* mice', which are mice that develop without otoliths but normal semi-circular canals, to demonstrate that the loss of the otoliths independently of the canals, can cause a dysfunction in spatial memory, particularly in the absence of visual information. It has been shown that such mice also exhibit abnormal exploration of the spatial environment (Blankenship et al. 2017), similar to mice with complete vestibular loss (Banovetz et al. 2021).

Spatial memory deficits for BVL rats with visual cues

We also demonstrated that rats with BVL exhibited spatial memory deficits even with visual information. After 6 weeks post-BVL, rats performed at a significantly poorer level in the radial arm maze task, another spatial memory task (Russell et al. 2003a, 2003b; this study combined chemical and surgical lesions). In the T maze task, the performance of the rats improved over time, but their performance was still below sham controls with the tympanic membrane removed, at 5 months post-BVL (Zheng et al. 2007, 2012a, 2012b; Figure 2).

Spatial memory impairment in light has been demonstrated with the radial arm maze and Y mazes in rats that were subjected to left then right, or right then left, unilateral chemical vestibular lesions using intratympanic sodium arsanilate (Besnard et al. 2012; Machado et al. 2012a, 2012b). In an attempt to assess attentional performance, we employed a 5 choice serial reaction time task (5- CSRTT), and observed that BVL rats exhibited significantly more incorrect responses and fewer correct responses than the control group. Nonetheless, they made the same number of omissions, and performed the task with a reduced latency (Zheng et al. 2009a; Figure 3). The lack of omissions in the surgical BVL group showed that they were capable of responding (i.e. not inhibited

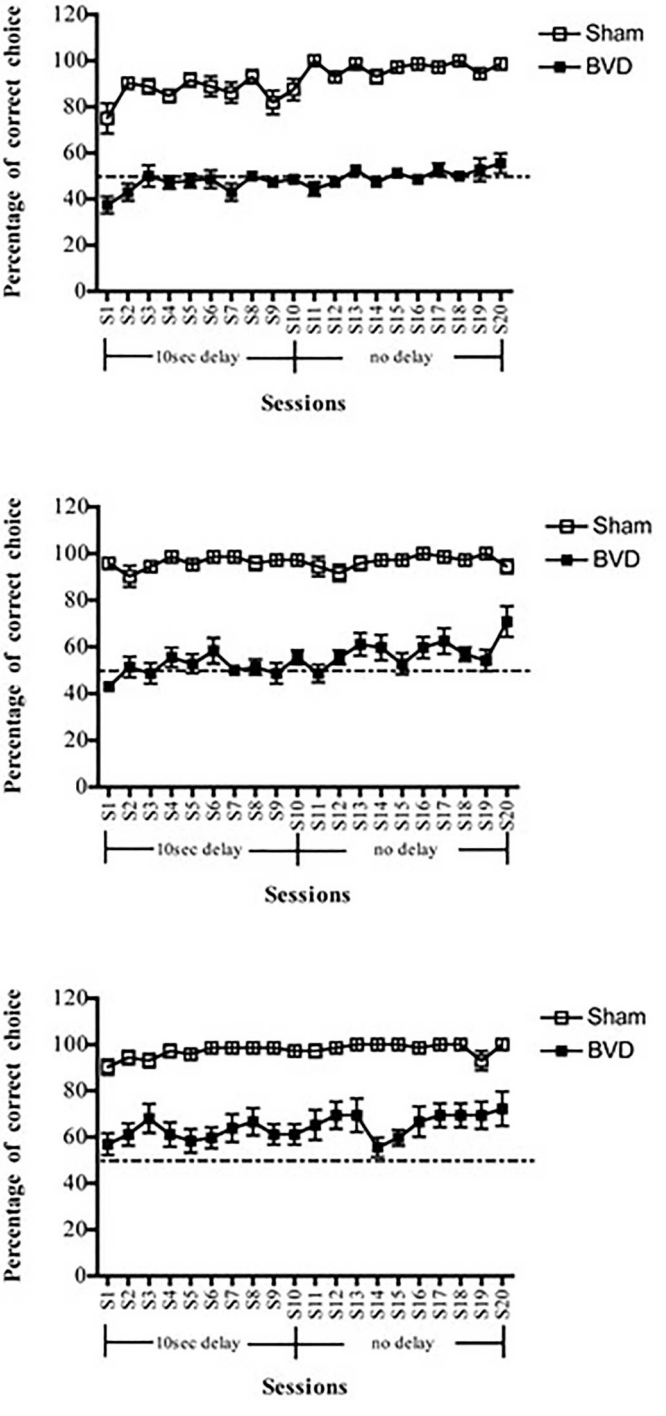

Figure 2. Percentage of correct choices in the T maze task for bilateral vestibular deafferentation (BVD) and sham surgery control animals at 3 weeks **A,** 3 months **B,** and 5 months **C**, post-op in a simple alternating T maze task. Symbols represent means and bars 1 SE of the mean. Reproduced with permission from Zheng et al. (2007).

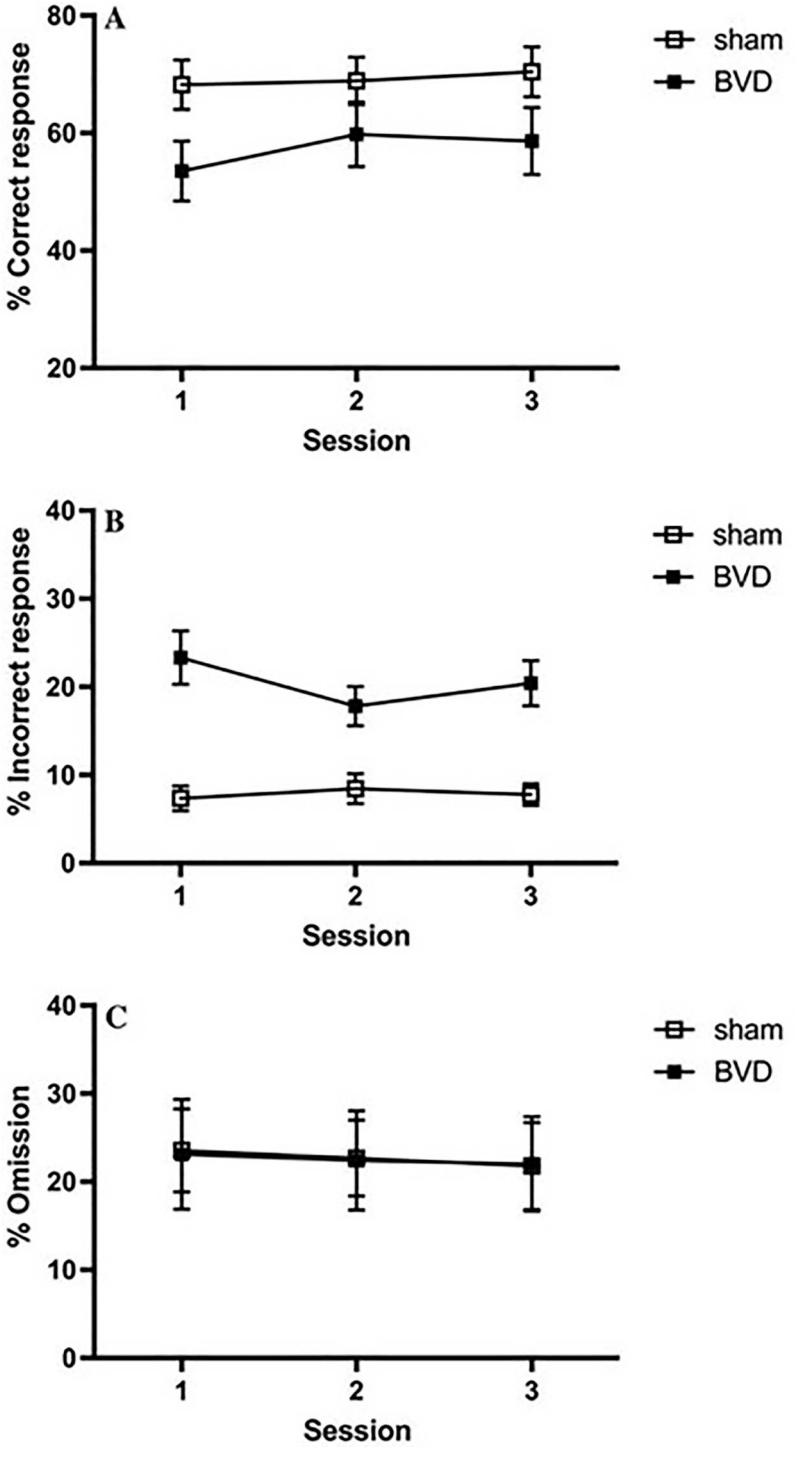

Figure 3. Percentage of correct responses **A,** incorrect responses **B** and omissions **C** for sham (open square) and BVD (closed square) rats after the animals reached the criterion in a 5 choice serial reaction time task. Data are expressed as mean ± s.e.m. Asterisks indicate significant differences. Reproduced with permission from Zheng et al. (2009b).

by ataxia) even though their responses were often incorrect. This was the first evidence from animals that attention was impaired following vestibular dysfunction, which is consistent with attentional deficits in vestibular patients (Sang et al. 2006; Jauregui-Renaud et al. 2008a; Jauregui-Renaud et al. 2008b). A number of studies have shown that mice with genetic otolithic deficits, such as the *tilted* mouse, also exhibit spatial memory deficits when visual information is available (Avni et al. 2009; Machado et al. 2012a; Yoder and Kirby 2014). These results highlight the significance of the otoliths for normal performance in memory tasks. Avni et al. (2009) showed, in the mutant *headbanger* mouse, which has abnormally elongated stereocilia, partially affecting both the canals and the otoliths, that they exhibited hyperactivity and disorientation in a spatial environment.

These results showed that BVL can have various effects in different cognitive tasks: the foraging task, radial arm maze task, Y maze and T maze and the 5-CSRTT. Nonetheless, all of these tasks rely on the use of visual cues, in which case oscillopsia would be expected to make the performance worse, and therefore the specific contribution of vestibular information could not be precisely delineated.

Effects of UVL and BVL in a spatial memory task without visual cues

For rats with surgical BVL who performed the foraging task in darkness, the spatial memory impairment was more severe than for surgical UVL (i.e. only one inner ear lesioned; Zheng et al. 2006, 2009; Figure 1). We found that rats with surgical UVL exhibited spatial memory impairment in darkness similar to those with BVL after a 3 month post-op, delay; however, they then performed similar to sham controls after a 6 month delay (Zheng et al. 2006). While BVL rats exhibited only a slight impairment in the foraging task in light, after a 5–6 month delay, their performance was much worse in darkness without visual cues (Zheng et al. 2009). This result suggests that in the absence of vision, rats rely mainly on vestibular cues in order to navigate spatially. Rats with BVL lesions were profoundly impaired in the foraging task in darkness after a 14 month delay (Baek et al. 2010), suggesting that complete removal of vestibular information may cause spatial navigation deficits; by contrast, the impairment caused by partial loss of vestibular function (i.e. UVL), may be reversible. These studies illustrate the fundamental significance of the vestibular system for spatial memory. Furthermore, the results from the trials without visual cues indicate that oscillopsia alone is not responsible for the spatial memory dysfunction.

Possible relationship between spatial memory deficits and locomotor hyperactivity

Many researchers have observed that rats with BVL show locomotor hyperactivity (Baek et al. 2010; Besnard et al. 2012; Goddard et al. 2008; Machado et al. 2012a; Russell, et al., 2003a, 2003b; Stiles et al. 2012; Zheng et al. 2009, 2012a, 2012b). It is, therefore, conceivable that this prevents rats with BVL from correct performance in cognitive tasks. In order to investigate this further, we used regression analyses to determine whether hyperactivity could predict the cognitive deficits exhibited in the foraging task. However, we found no statistically significant relationship between the BVL rats' poor performance

in the foraging task and their hyperactivity (Baek et al. 2010). We have also investigated this question using multiple linear and random forest regression and found that hyperactivity was not related to the performance deficits in a spatial T maze alternation task. The most effective predictors of poor performance were BVL itself and the duration of open field maze rearing (Smith et al. 2013). Therefore, the spatial memory deficits of BVL rats cannot simply be explained by their hyperactivity.

Possible relationship between spatial memory deficits and anxiety

Many patients with vestibular dysfunction have affective disorders and it is conceivable that anxiety and depression have some causal role in the cognitive dysfunction associated with vestibular lesions (Balaban and Thayer 2001; Balaban 2002; Staab 2006).

It is more difficult to dissociate anxiety/depression from cognitive deficits presenting in patients with vestibular disorders; however, in animal studies, there have been some attempts to do this. Using the black and white box test of anxiety, Machado et al. (2012a) investigated whether BVL rats exhibited increased anxiety which could be reversed by the benzodiazepine anxiolytic drug, diazepam. The diazepam significantly decreased the animals' anxiety; however, it did not affect their deficits in the radial eight-arm maze spatial memory task. If the memory deficits were caused by anxiety, then a drug that reduces anxiety should also have reduced the memory deficits. This result implies that the rats' anxiety is independent of their spatial memory deficits.

Vestibular versus auditory damage

As mentioned previously, it is difficult to avoid damage to the cochlea when lesioning the vestibular system, because they are located so closely. Consequently, it becomes difficult to exclude the possibility that hearing loss rather than vestibular loss is responsible for the cognitive deficits. Noise trauma has been reported to cause hippocampal place cell dysfunction (Sakurai 1990, 1994; Goble et al. 2009). We have often used sham animals without their tympanic membranes so that sound could not be transmitted effectively to the ossicles (the malleus, incus and stapes) and then transduced by the cochlear hair cells. This can only serve as a partial auditory control because some sound will still be transmitted to the cochlea. However, we have consistently observed that rats who have the tympanic membranes removed, with their vestibular systems intact, performed more effectively in spatial memory tasks than animals with vestibular loss (Baek et al. 2010; Zheng et al. 2006, 2007, 2009, 2009b, 2012a, 2012b). Therefore, hearing loss is unlikely to be responsible for the spatial memory deficits in rats with BVL. Although hearing loss can cause cognitive deficits in humans, patients without hearing loss and with vestibular dysfunction still exhibit cognitive deficits (e.g. Brandt et al. 2005; see Smith 2022 for a review). Animal studies which have used aminoglycoside antibiotics to lesion the vestibular or auditory systems (i.e. streptomycin, neomycin, gentamicin), have reported that the effects of auditory and vestibular lesions have different effects on cognition (Schaeppi et al. 1991). Using the radial arm maze task, rats that received streptomycin, which is toxic to the auditory *and* the vestibular systems, exhibited impaired working memory; on the other hand, rats that received neomycin, which is mainly toxic to the auditory system, performed normally (Schaeppi et al. 1991). In

general, this is a difficult issue because disorders such as Meniere's Disease often present with both vestibular (e.g. vertigo) and auditory (e.g. tinnitus) symptoms, and some aminoglycosides such as gentamicin can lesion both auditory and vestibular hair cells.

There has been debate as to whether spatial memory dysfunction is the only cognitive deficit in animals caused by vestibular loss. We have demonstrated that BVL can also cause attention deficits (Zheng et al. 2009) and deficits in an object recognition memory task (Zheng et al. 2004). Nonetheless, others have not observed object recognition memory deficits (Besnard et al. 2012); therefore, this issue remains to be resolved.

Vestibular lesions and spatially responsive neurons

In the 1990s, bilateral vestibular lesions caused by intratympanic tetrodotoxin (TTX), were shown to cause a disordered firing of thalamic head direction cells, which are known to be important in encoding sense of direction (Stackman and Taube 1997 for a review). The activity of head direction cells also became abnormal during inverted locomotion (Calton and Taube 2005) and with selective loss of otolithic (Yoder and Taube 2009) or semi-circular canal function (Muir et al. 2009; Valerio and Taube 2016). Using the same method to reversibly lesion the peripheral vestibular system bilaterally, Stackman et al. (2002) reported that bilateral vestibular loss caused fragmented firing of hippocampal place cells. Hippocampal place cells, in addition to entorhinal grid cells, are known to be pivotal to the brain's ability to navigate through the spatial environment, and two Nobel Prizes were awarded for these discoveries in 2014 (see Jeffery 2024 for a review). A striking feature of Stackman et al.'s (2002) finding was that the abnormal firing of the place cells was immediate; however it started to recover as the TTX wore off. This suggested that hippocampal place cells rely on continuously updated information from the vestibular system and delayed structural changes in the hippocampus were unnecessary for the place cells to become dysfunctional. Using permanent surgical BVL, we also found that the aberrant place cell activity did not recover even 6 weeks later (Russell et al. 2003b; Figure 4). More recently, Harvey et al. (2018) have demonstrated that place cell function is abnormal in mice with a genetic otolith dysfunction.

Theta rhythm in the hippocampus is a large amplitude, approximately 5–12 Hz sinusoidal EEG rhythm which serves to integrate the firing of hippocampal place cells (Hasselmo 2005; Vertes 2005). Very few studies have examined the effects of vestibular loss on theta rhythm. Although Stackman et al. (2002) observed no changes in one rat with BVL using intratympanic TTX, we used permanent surgical BVD to investigate the effects of vestibular loss on theta rhythm (Russell et al. 2006). In contrast to Stackman et al. (2002), we found that hippocampal theta rhythm was severely disrupted in terms of the power of the sinusoidal character of the waveform. Although the BVD animals were hyperactive, theta rhythm was abnormal across a wide range of velocities. We have replicated these findings in a study in which we tried, but failed, to reverse the spatial memory and emotional deficits caused by BVD by electrically stimulating the septum in order to generate an artificial theta rhythm (Neo et al. 2012). Tai et al. (2012) also demonstrated that rats with BVL due to intra-tymapnic sodium arsanilate exhibited a decrease in theta power.

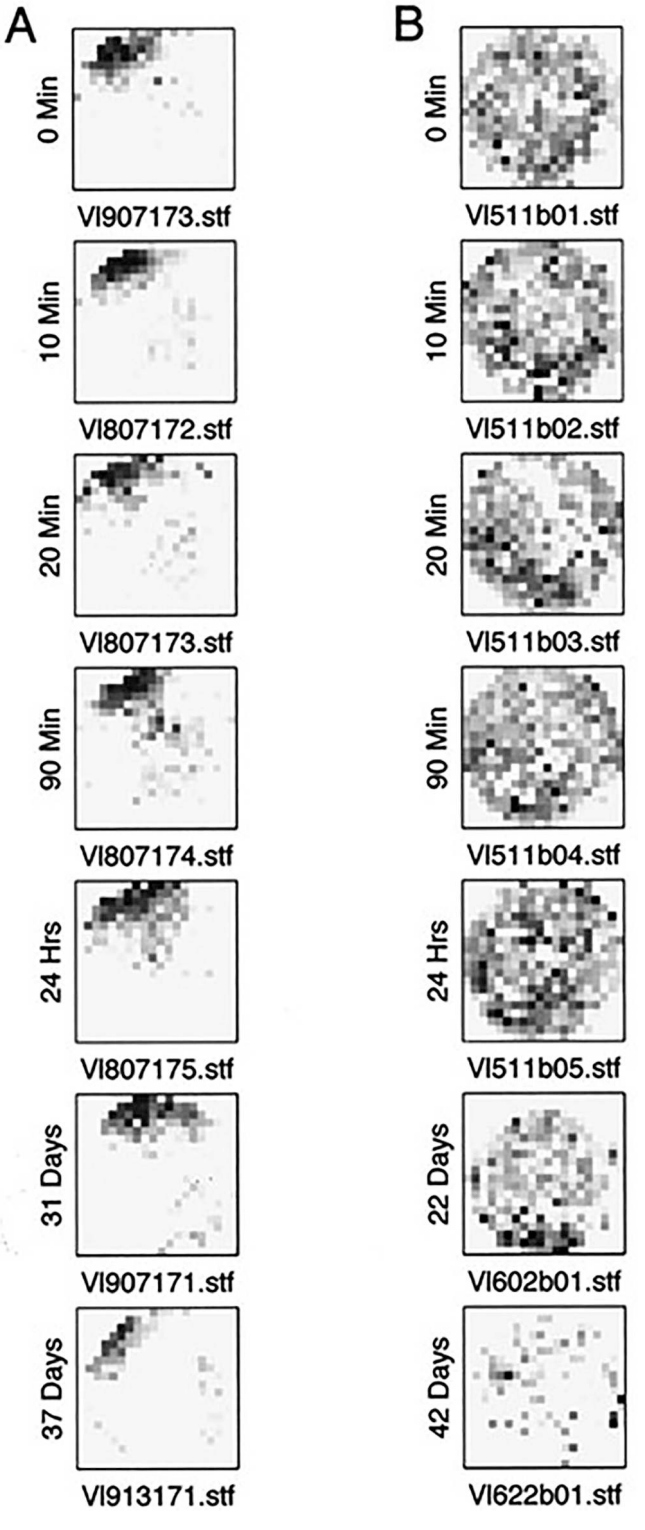

Figure 4. Firing rate maps for the cells recorded over a 6 week period. Control complex spiking cell. *B*, Lesion complex spiking cell. Reproduced with permission from Russell et al. (2003b).

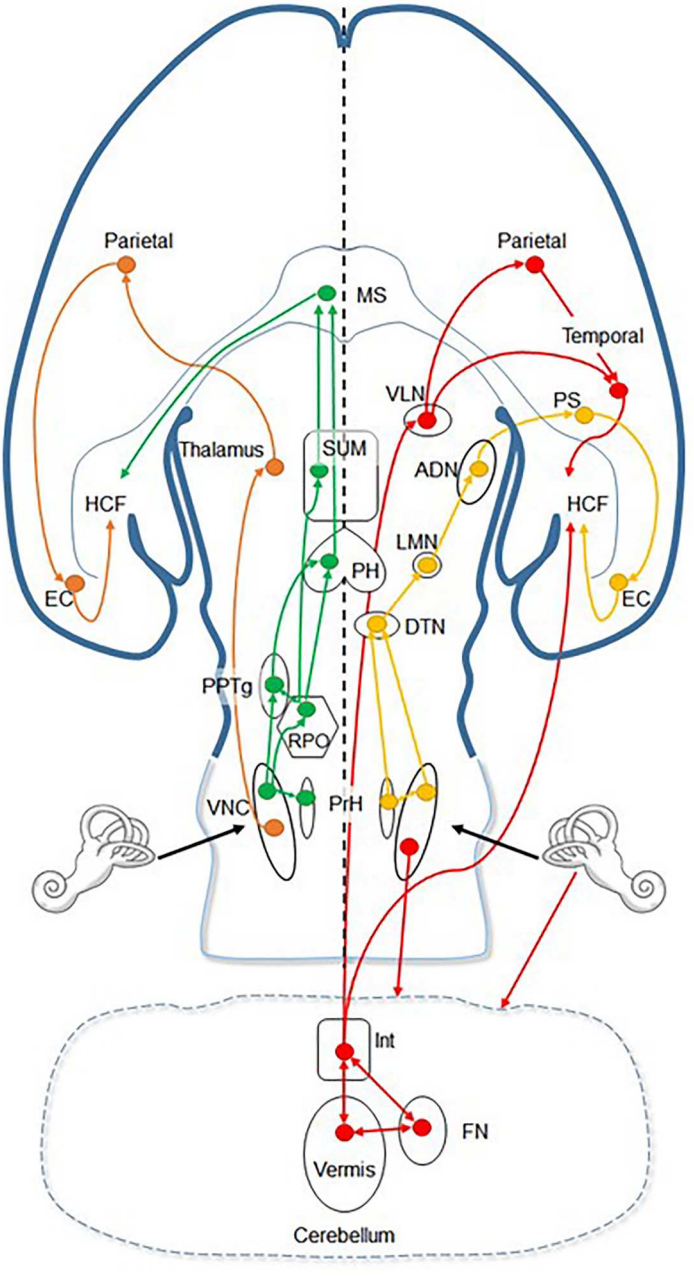

Figure 5. Proposed pathways from the peripheral vestibular organs to the hippocampus on a diagram of a horizontally sliced rat brain. Thalamo-cortical pathway (*brown*). Theta generating pathway (*green*). Cerebello-cortical pathway (*red*). Head direction path-way (*yellow*). *ADN* anterior dorsal nucleus, *DTN* dorsal tegmental nucleus, *EC* entorhinal cortex, *FN* fastigial nuclei, *HCF* hippocampal formation, *Int* interpositus nuclei, *LMN* lateral mammillary nucleus, *MS* medial septum, *Parietal* parietal cortex, *PH* posterior hypothala – mus, *PrH* prepositus hypoglossi, *PPTg* pedunculopontine tegmen – tal nucleus, *PS* postsubiculum, *RPO* reticularis pontis oralis, *SUM* supramammillary bodies, *Temporal* temporal cortex, *VLN* ventral lat – eral nucleus of the thalamus, *VNC* vestibular nuclei. Reproduced with permission from Aitken et al. (2017).

Taken together, these animal studies support the hypothesis that vestibular information is pivotal for the generation of normal hippocampal function and spatial cognition (Wiener and Berthoz 1993; Berthoz 1996; McNaughton et al. 1996; McNaughton et al. 1996; Etienne and Jeffery 2004; Smith et al. 2005; Smith et al. 2009; Smith et al. 2010).

Information transmission from the vestibular inner ear to the hippocampus

How does vestibular information reach the hippocampus? The answer to this question Is incomplete, although it is likely that there are multiple neural pathways involved. Electrical stimulation of one vestibular labyrinth or the vestibular nucleus in the brainstem has been demonstrated to generate field potentials, single neuron activity and neurotransmitter release in the hippocampus. These responses occur with long latencies, suggesting many synapses are involved (Cuthbert et al. 2000; Hitier et al. 2021; Horii et al. 1994, 2004; Figure 5). Stimulation of the human vestibular system has also been shown to cause hippocampal activation (Vitte et al. 1996; De Waele et al. 2001); glucose uptake is reduced in the hippocampus in acute vestibular neuritis patients (Bense et al. 2004). The thalamus is an important integrative relay for ascending vestibular information (Figure 5).

However, there may be a number of different pathways from the vestibular nucleus and cerebellum to the hippocampus (Smith 1997; Hitier et al. 2021; see Shinder and Taube 2010 and Hufner et al. 2011 for reviews). Selective electrical stimulation of the anterior, horizontal, or posterior semi-circular canals or the utricle or saccule, has been shown to activate many subregions of the hippocampus (Hitier et al. 2021). Furthermore, the hippocampus is only part of the limbic-neocortical network involved in spatial memory (Gu et al. 2007; Guldin and Grusser 1998; Hanes and McCollum 2006; Lopez and Blanke 2011; Shinder and Taube 2010; Figure 5). In humans, galvanic vestibular stimulation (GVS) during fMRI has demonstrated significant activation of the posterior insula, the retroinsular regions, the superior temporal gyrus, 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 as well as the hippocampus (Lobel et al. 1998; see Karnath and Dieterich 2006 for a review).

Conclusions

Over the last 24 years, our behavioural and electrophysiological studies have contributed to a substantial body of data indicating that a loss of vestibular function causes cognitive disorders, in particular related to memories for space, that are related to the way that parts of the brain like the hippocampus normally rely on information about movement from the vestibular system. This research has significant implications for the treatment of dementia, and the probability of falls in the elderly, who suffer from age-related vestibular dysfunction ('presbyvestibulopathy').

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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