Review

Does vestibular damage cause cognitive dysfunction in humans?

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Abstract. For more than a decade, evidence from animal studies has suggested that damage to the vestibular system leads to deficits in spatial navigation which are indicative of impaired spatial learning and memory. More recently, direct evidence has emerged to demonstrate that humans with vestibular disorders exhibit a range of cognitive deficits that are not just spatial in nature, but also include non-spatial functions such as object recognition memory. Vestibular dysfunction has been shown to adversely affect attentional processes and increased attentional demands can worsen the postural sway associated with vestibular disorders. Recent MRI studies also show that humans with bilateral vestibular damage undergo atrophy of the hippocampus which correlates with their degree of impairment on spatial memory tasks. These results are consistent with those from animal studies and, together, suggest that humans with vestibular disorders are likely to experience cognitive dysfunction which is not necessarily related to any particular episode of vertigo or dizziness, and therefore may occur even in patients who are otherwise well compensated. These findings may be related to the observation that patients with vestibular deficits experience a high incidence of depression and anxiety disorders.

Keywords: Vestibular damage, cognition, vestibular compensation

1. Introduction

The effects of unilateral or bilateral peripheral vestibular damage on ocular motor and postural reflexes in humans have been studied extensively (see [2,13] for reviews). However, over the last decade, there has been a steady accumulation of evidence to suggest that vestibular lesions may also lead to cognitive deficits, including deficits in attention, learning and memory, that are not necessarily directly attributable to the reflexive symptoms and perceptual abnormalities associated with the damage. Rather, there is increasing evidence that the loss of vestibular sensory information may alter, perhaps permanently, the way that cognitive processing areas of the brain integrate spatial and non-spatial information (see [59] for a review of the early literature).

Despite the process of vestibular compensation that usually occurs following vestibular damage, many of the ocular motor and postural symptoms either do not compensate or else compensate incompletely. This is particularly true of the vestibulo-ocular reflexes (VORs), which never recover their normal response to high acceleration stimuli (see [12,13] for reviews). It can therefore be difficult to distinguish between the perceptual consequences of ongoing reflex deficits and deficits in cognition itself (i.e., the processes of attention, learning, memory, analysis and mental imagery),

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unless suitable controls are used. There is also the possibility that cognitive deficits appear in certain situations because of the demands that maintaining compensation of reflex deficits places on cognitive function (e.g., [51]). The aim of this mini-review is to critically evaluate the current evidence that vestibular damage leads to cognitive dysfunction in humans. We will focus specifically on cognitive studies in humans with vestibular dysfunction; animal studies will be mentioned only briefly since these have been reviewed in detail elsewhere [59,60,64].

1.1. Animal studies of the effects of vestibular damage on learning, memory and hippocampal function

Since Beritoff [3], numerous theorists have considered the possibility that vestibular information is used to construct spatial maps of the environment and to navigate from one place to another (see [3,4,6,18,43, 44,50,60,64] for reviews). This notion was supported by animal studies which demonstrated that unilateral or bilateral vestibular damage resulted in impaired performance by rats and guinea pigs in various radial arm maze, water maze or foraging tasks [9,34,42,45,48,54, 62,66]. In some of these studies, the impaired performance was confounded by the severity of the vestibular symptoms soon after an acute peripheral vestibular lesion; however, in others, the studies were conducted months following the lesion, when partial compensation had occurred, and therefore the results were unlikely to be due simply to loss of motor control (e.g., [54,62,66]). In fact, in some studies, rats with bilateral vestibular lesions were found to be hyperactive [54,66].

Many early anatomical and electrophysiological studies demonstrated that there are several pathways from the vestibular nucleus to areas of the limbic system and neocortex concerned with learning and memory (see [4,20,59,67] for reviews). Considerable interest focussed on the hippocampus, due to its recognised role in spatial information processing. In particular, hippocampal 'place cells' in region CA1 were known to respond to specific locations in space which the animal had explored (see [18,43,44] for reviews). Numerous studies showed that the response of place cells could be modulated by vestibular stimulation (e.g., [21,22, 68]; see [59] for a review). Studies by Horii and colleagues [31–33,46] also showed that electrical stimulation of the vestibular nucleus could evoke the release of acetylcholine in the hippocampus; later studies showed that hippocampal field potentials could be evoked by electrical stimulation of the labyrinth [14,28] and that the firing of complex spike cells (likely to be place cells) in CA1 could be evoked by electrical stimulation of the medial vestibular nucleus [30]. Studies in alert behaving rats demonstrated that bilateral vestibular deafferentation could severely disrupt the normal function of thalamic 'head direction cells', which appear to encode the directional heading of the animal in space [63]. The response of hippocampal place cells was also disrupted, even 6 weeks following the lesion [55,61]. Hippocampal theta rhythm was also reduced in power [56] and hippocampal slices removed from rats that had received a previous unilateral labyrinthectomy showed a reduction in the size of field potentials in CA1 evoked by electrical stimulation of the Schaffer collaterals [77]. Furthermore, peripheral vestibular lesions were shown to produce significant neurochemical changes in the hippocampus, including changes in nitric oxide synthase and N-methyl-D-aspartate receptor subunit expression, that last for weeks following the damage [38, 39,74,76,78–80]. Neurochemical changes have also been found in the perirhinal and entorhinal cortices following vestibular damage [37].

A major limitation of the behavioural studies in animals is the fact that, of necessity, they have all used locomotion as a dependent variable; even though the animals were clearly capable of moving in a maze environment so long after the vestibular lesion, it is difficult to completely exclude the possibility that the impaired performance was partially due to the effects of the vestibular damage on locomotor control. Since movement of the eyes or limbs is virtually the only way of measuring cognition in animals, this is a difficult limitation to overcome. Another limitation of all of these studies is that the animals sustained auditory damage during the vestibular lesion, and therefore the potential contribution of the hearing loss is unclear. There is evidence to suggest that auditory information is not important for hippocampal place cell function in rats [29, 53]; however, the issue has not been fully investigated. This potential confound is also a problem for many of the human studies discussed below.

2. Evidence for hippocampal changes in humans with vestibular damage

A number of studies have shown that stimulation of the vestibular system in humans results in changes in activity in the hippocampus and other related areas of the medial temporal lobe (e.g., [2,5,16,65]). However,

few studies have analysed either medial temporal lobe function or structure following vestibular damage in humans. In a study so far published only in abstract form, Bense et al. [2] have shown that, during the acute stage of recovery from vestibular neuritis, cerebral glucose metabolism (measured using PET) was increased in the parieto-insular vestibular cortex, the anterior cingulate gyrus, the hippocampus, the posterolateral thalamus and the ponto-mesencephalic brainstem. During caloric stimulation, patients with bilateral vestibular failure showed a small activation in the contralateral posterior insula [2].

In the first study of its kind, Brandt et al. [8] have reported that neurofibromatosis type 2 (NF2) patients with bilateral vestibular failure, which show deficits in spatial memory [57], exhibited atrophy of the hippocampus (measured using MRI). Surprisingly, the hippocampus was the only area of the brain to show such atrophy, and the degree of atrophy correlated with the degree of impairment in spatial memory. According to the Weschler Memory Scale (WMS), the patients had similar general intelligence before and after the loss of vestibular function. Whether the decrease in the volume of the hippocampus was due to cell death or changes in hippocampal cytoarchitecture (such as the changes in dendritic arborization that occur with chronic stress), remains to be seen.

Although the effects of bilateral vestibular damage have not yet been investigated, it is interesting to note that in hippocampal slices removed from rats that had compensated for unilateral vestibular deafferentation, Zheng et al. [77] observed markedly reduced field potentials indicative of a decrease in electrical excitability. If cell death does occur in the hippocampus after vestibular damage, it would be remarkable given that there is little evidence for cell death in the vestibular nucleus under such conditions (e.g., [15]). Chronic stress has been shown to cause cell death in the hippocampus (see [41] for a review). While evidence from animals suggests that stress levels, as indicated by salivary or blood glucocorticoid concentrations, decrease rapidly after acute vestibular damage [24,36,73], it is possible that recurring vestibular symptoms in humans are associated with continuously high levels of cortisol which could lead to hippocampal cell death [58]. However, this would not explain why, in some cases, well compensated patients (i.e. no complaints of dizziness or imbalance) still appear to exhibit cognitive deficits (see below) [51].

3. Clinical evidence for cognitive dysfunction in humans following vestibular damage

In general, the available clinical evidence can be divided into studies in which some cognitive function is measured through a form of motor activity to which the vestibular reflexes are known to contribute, such as walking, and those studies in which cognitive function is measured through another kind of motor performance, such as verbal communication, writing or movement of a cursor on a computer screen. Needless to say, as direct measures of cognitive function, the latter studies are easier to interpret because of the possibility that residual reflex deficits contribute to apparent cognitive deficits in the former studies (most of which were not designed to evaluate cognition *per se*). Standard neuropsychological tests, such as the Weschler Memory Scale (WMS), have been used to evaluate memory [27]; specific WMS tests such as Visual Reproduction Tests are designed to assess memory for visual information [27]. The Digit Span Test is a part of the Weschler Intelligence Test which specifically measures attention: random numbers are read forwards and backwards, with the span between the digits becoming increasingly larger, and the subject must accurately repeat the digit sequences [27]. More recent studies have used 'virtual', computerized versions of the Morris water maze task, to assess memory for places in space (i.e., spatial memory), without the subject having to move anything but a cursor [56].

3.1. Path trajectory studies

A number of studies have reported that patients with vestibular impairment have difficulty with 'path integration tasks' in which they have to learn to walk a specific path through the environment, either with their eyes closed or open. Patients with Meniere's disease, benign paroxysmal positional vertigo (BPPV) or chronic vestibulopathy exhibit errors in such tasks not seen in labyrinthine-intact humans (e.g., [7,10,11,49]). These deficits were not due simply to motor dysfunction or an acute vertiginous episode, but seemed to be due to deficits in learning and remembering tasks that are spatial in nature. Peruch et al. [49] studied 8 unilateral vestibular deficient patients with Meniere's disease who received a unilateral vestibular neurectomy to relieve vertigo but preserve hearing. During the first week of post-operative recovery, turn error during path integration tasks was significantly greater than for controls. Although in this case the auditory contribution

to the performance deficit can be excluded, it is difficult to completely disentangle the 'cognitive' aspect of the dependent variable from the vestibulospinal reflex contributions. These studies were, of course, specifically designed to evaluate path integration, not cognition itself, and at the very least performance in such tasks probably represents a complex combination of cognitive and sensori-motor function [7].

3.2. Studies of attention, reaction time and memory

One of the first studies of cognitive function in patients with vestibular disorders was reported by Grimm et al. [27], who detailed perceptual and memory deficits in patients with perilymph fistula syndrome (PLFS). All of the patients in the study had confirmed positional vertigo and perilymph fistulae, which in most cases were confirmed at the time of surgery. It was presumed that the fistula resulted from head trauma, chronic ear infection or acceleration forces that caused a tear in the round or oval window membranes and a consequent leakage of perilymphatic fluid into the middle ear. At the same time, otoconia dislodged from the utricle accumulated in the cupula of the posterior canal ampulla, causing BPPV. From a total sample of 102 patients, more than 95% suffered from long-term 'disorientation' in any situation involving conflict between visual and vestibular information, such as movement of the visual field in the absence of self-motion [27].

The surprising observation was that more than 85% of the patients reported memory loss of some sort. In a quantitative study of a sub-sample of these patients, performance on digit symbol, block design and picture arrangement was in the impaired range despite a normal level of intellectual function. Although performance on the WMS Information, Digit Span and Visual Reproduction tests was normal, scores on auditory recall and learning and paired associate learning were all below the normal range. Interestingly, many of these patients also suffered from affective symptoms such as anxiety and depression [27]. In the case of PLFS, it is difficult to exclude the contribution of auditory dysfunction to the cognitive deficits observed, since vestibular and auditory dysfunction are both part of the syndrome and occur together.

Risey and Briner [52] reported that patients with vertigo of central origin exhibited significant impairments in counting backwards by two and in mental arithmetic ('dyscalculia'). The subjects also showed deficits in central auditory processing, therefore there may have been an auditory component to the phenomenon. Yard-

ley et al. [71] have also reported that patients with vestibular dysfunction performed significantly worse than controls on a mental arithmetic task when they were being passively oscillated and asked to monitor their orientation. In another study, Yardley et al. [70] measured the postural stability of 48 patients with a variety of vestibular disorders on a moving platform while they were required to perform various spatial and non-spatial tasks. They found that as the balancing task became more difficult, the subjects' reaction times became slower and their accuracy poorer on spatial and non-spatial mental tasks. The authors suggested that the process of monitoring orientation can make substantial demands on cognition in a vestibular deficient patient and that this may lead to poorer performance in a cognitive task [71]. By contrast, Andersson et al. [1] reported no significant effects of different balance conditions on performance in cognitive tasks by vestibular deficient patients; however, when attention was focussed on body sway, significantly greater sway was observed during the cognitive tests when there was no calf stimulation.

More recently, Redfern et al. [51] studied 15 patients with unilateral vestibular loss. All of the patients were well compensated, with no complaints of dizziness and all had normal hearing in their remaining ear. The subjects were tested in 4 postural conditions: 1) seated; 2) standing with a fixed floor and a stable visual environment; 3) standing on a sway-referenced floor with a stable visual environment; and 4) standing on a pseudo-random translating floor with a stable visual environment. During these 4 postural conditions, the subjects were given either an auditory simple reaction time task, an auditory choice reaction time task, or an inhibitory reaction time task. Compared to controls, the reaction times were significantly longer for patients in all tasks, and the difference increased with the complexity of the task. However, perhaps the most surprising result was that the patients' reaction times were longer even in the seated condition without any sway, and this difference was much greater for the more complex cognitive tasks (see Fig. 1). Since there was no postural challenge in this situation, this result seems to provide direct evidence for a cognitive deficit which is not confounded by any movement to which the vestibular reflexes would normally contribute. In the auditory simple reaction time task, the subjects had to respond with a simple button press when they heard a particular tone. In the complex choice reaction time task, they had to press a button with their dominant hand and another button with their non-dominant hand. In the inhibitory reaction

time task, they had to respond to a visual 'go' stimulus, unless they heard a 'stop' tone through the headphones. The possibility that the patients could not perceive the stimuli as accurately as the controls cannot be totally excluded. However, the fact that subjects had only to press a button in response to a stimulus of varying complexity and the patients performed so poorly even while seated, suggests that some aspect of cognitive function, i.e. attention, memory or ability to analyse information, was impaired. Importantly, the differences in hearing between the patients and controls could not account for the results. The patients were receiving the auditory information only through the unoperated ear; however, control studies using monaural versus binaural presentation in the control subjects showed no differences in reaction times. Furthermore, the patients showed similar responses in the complex choice reaction time and inhibitory reaction time tasks, even though in the latter the response stimulus was visual. Redfern et al. [51] considered the issue of whether cognitive performance might be decreased as a direct result of the vestibular damage or because of the demands that maintaining the compensated state places upon cognitive processes. They suggested that if the latter were true, one might expect that cognitive deficits would be greater in patients who have not compensated. In the study of Yardley et al. [70], the patients were currently complaining of dizziness; however, in Redfern et al's [51] study, all of the patients were well compensated (i.e., they did not complain of dizziness or imbalance) and yet still displayed deficits in reaction time.

Schautzer et al. [57] studied the performance of 10 patients with bilateral vestibular loss as a result of NF2 and 10 sex- and age-matched controls, on a computerized virtual water maze task. The task was used to evaluate the subjects' ability to successfully navigate to a particular place in space, similar to the real water maze task, but had the advantage that the subjects only had to move a cursor on a computer screen using a keyboard. Only 5 of the 10 NF2 patients could directly navigate to the hidden platform on the screen, compared to 10/10 for the controls. Patients exhibited longer latencies to navigate to the platform; during the probe trial in which there was no platform, whereas the controls spent most of their time in the quadrant where the platform had been previously, the NF2 patients spent only 25% of their time in that quadrant (see Fig. 2). Since the Morris water maze is a standard and reliable test for spatial learning and memory, this study provides evidence that patients with bilateral vestibular failure experience deficits in memorising spatial locations. The fact that
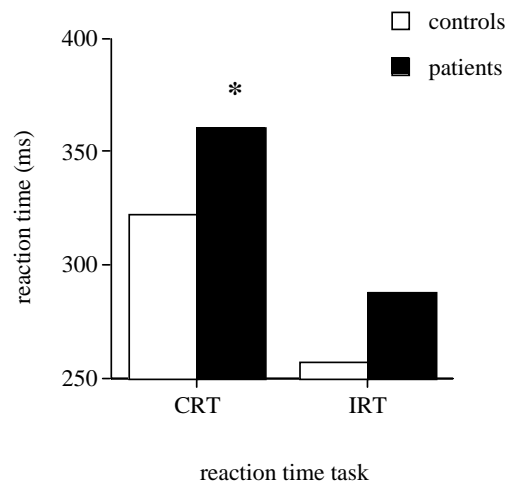

Fig. 1. Complex reaction time data regraphed from Redfern et al. [51], showing the response of controls and patients with unilateral vestibular loss on a choice reaction time task (CRT), and an inhibitory reaction time task (IRT), *while seated* (i.e. without any postural challenge), Bars represent means calculated from Fig. 2 in Redfern et al. [4], ∗ = significant difference between the mean reaction times for controls and patients, at < 0.05.
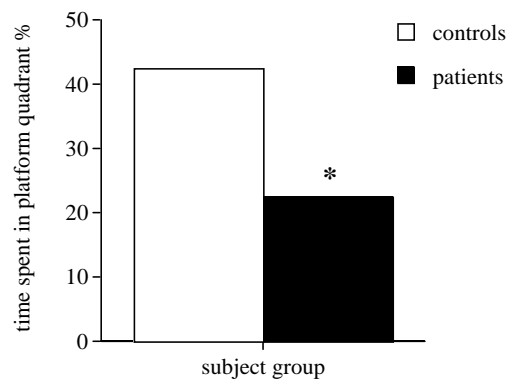

Fig. 2. Data regraphed from Schautzer et al. [57], showing the time spent in the previously correct platform quadrant for controls and patients with bilateral vestibular loss. Bars represent means calculated from Fig. 3 in Schautzer et al. [57], ∗ = significant difference between controls and patients, at $p < 0.01$.

the patients were not impaired in cued navigation tasks in which the platform was visible, suggests that the deficit was not due simply to deficits in motor control, visual perception or motivation [57]. Only one of the NF2 patients had complete hearing loss, and therefore it is unlikely that deafness contributed to the results.

Despite these studies, Gizzi et al. [23] have argued that there is no causal connection between vestibular dysfunction and cognitive impairment. They studied 200 patients at an outpatient balance disorders clinic, using the Neurobehavioral Symptom Inventory (a ques-

tionnaire which measures a range of neurological and psychological symptoms), and found that cognitive complaints were more common in dizzy patients with a history of brain trauma and that there was no significant correlation between the diagnosis of vestibular dysfunction and the frequency of cognitive complaints. However, this study was epidemiological in nature and involved no quantitative analysis beyond the frequency of cognitive dysfunction as assessed by the inventory.

4. Implications for treatment

Taken together, the available studies provide substantial evidence that patients with vestibular disorders experience cognitive dysfunction, some of which involves spatial information processing, and some of which is non-spatial. Studies such as that by Redfern et al. [51] make it unlikely that the cognitive deficits are due to motor dysfunction or deafness. The use of cued virtual navigation control tasks such as those employed by Schautzer et al. [57] excludes the possibility that the spatial memory deficits are due to problems with vision, motor control or motivation. Although the results of Brandt et al. [8] suggest that the hippocampus is dramatically affected by bilateral vestibular damage, it is important to recognise that the non-spatial deficits are unlikely to be due to changes in the hippocampus. For example, Mumby [47] has argued that non-spatial memory such as object recognition memory is more likely to be related to areas like the perirhinal cortex. In this respect it is interesting to note that deficits in object recognition memory and exploration have been reported 3 and 6 months following bilateral vestibular damage in rats [75], and neurochemical changes have also been found in the perirhinal and entorhinal cortices following peripheral vestibular damage [37]. It is therefore likely that many areas of the limbic system and neocortex undergo reorganisation following vestibular damage [5].

4.1. Connection with anxiety and agoraphobia

It is well established now that patients with vestibular disorders experience a high incidence of depression and anxiety disorders, including agoraphobia [17,19, 58,69,72]. Is there a connection between the cognitive effects of vestibular damage in humans and emotional disorders? Godemann et al. [25] have reported that patients with vestibular disorders exhibit a high frequency of dysfunctional and 'catastrophic' cognitions,

that might lead to anxiety. Aside from the obvious possibility that patients with cognitive problems secondary to vestibular damage develop anxiety disorders because of the difficulties that their symptoms present in daily life, it is also conceivable that some of the emotional changes are due to the direct effects of vestibular damage in the hippocampus. It has been argued that the hippocampus is as much an emotional as a cognitive processing center (see [26] for a review). These two views of the hippocampus are, of course, not mutually exclusive, since most memories have emotional value and it is logical that spatial memories would be represented in the brain with an emotional grade. Our recent studies of rats with bilateral vestibular damage suggest that, even 6 months following the lesion, they display a lack of interest in exploration and, if given the opportunity, will remain in a concealed home cage rather than exploring for food in a foraging task [75]. Whether this is related to agoraphobia in humans with vestibular damage remains to be seen.

4.2. Use of cognitive therapy in rehabilitation

If patients with vestibular disorders suffer from cognitive deficits, then it is possible that cognitive and vestibular therapies might be useful in alleviating these symptoms. Johansson et al. [35] used cognitive behavioral therapy with vestibular rehabilitation in 9 patients with dizziness, and reported a significant decrease in symptoms. The intervention lasted 7 weeks with 5 weekly group sessions and the dizziness was assessed using walking time, response to provocative head movements, and the Dizziness Handicap Inventory (a standardized questionnaire which quantifies dizziness symptoms). If the cognitive burden of maintaining a compensated state is an important factor [51], it is conceivable that cognitive training could be of significant benefit in improving performance in divided attention situations. The virtual water maze tasks used by Brandt et al. [8,57] might also be extended for the purposes of retraining in spatial navigation, and incorporated into a vestibular rehabilitation programme [35]. During rehabilitation, therapists could also attempt to use the constructs of divided attention in an attempt to further rehabilitate people with vestibular dysfunction. Persons could be asked to multitask with a verbal cognitive task in order to attempt to optimize the person's ability to perform two skills at the same time without significant degradation of the skills. Examples could include walking and talking [40], where poor performance has been related to fall risk in older persons.

Acknowledgements

References

[1] G. Andersson, J. Hagman, R. Talianzadeh, A. Svedberg and H.C. Larsen, Dual-task study of cognitive and postural interference in patients with vestibular disorders, *Otol Neurotol.* **24** (2003), 289–293.

[2] S. Bense, P. Bartenstein, M. Schwaiger, P. Schlindwein, T. Stephan, T. Brandt and M. Dieterich, Brain activation studies in patients with vestibular neuritis and bilateral vestibular failure, *J. Vestib. Res.* **14** (2004), 151.

[3] J.S. Beritoff, *Neural Mechanisms of Higher Vertebrates*, Little, Brown and Co., Boston, 1965.

[4] A. Berthoz, How does the cerebral cortex process and utilize vestibular signals? in: *Disorders of the Vestibular System*, R. Baloh and G.M. Halmagyi, eds, Oxford University Press, New York-Oxford, 1996, pp. 113–125.

[5] A. Berthoz, The superior temporal gyrus, the retrosplenial cortex and the hippocampal formation: A fundamental network for vestibular induced spatial orientation and disorientation and for compensation of vestibular deficits, *J. Vestib. Res.* **14** (2004), 150–151.

[6] A. Berthoz, I. Israel, R. Georges-Francois, R. Grasso and T. Tsuzuku, Spatial memory of body linear displacement: what is being stored? *Science* **269** (1995), 95–98.

[7] L. Borel, F. Harlay, C. Loopez, J. Magnan, A. Chays and M. Lacour, Walking performance of vestibular-defective patients before and after unilateral vestibular neurotomy, *Behav. Brain Res.* **150** (2004), 191–200.

[8] T. Brandt, F. Schautzer, D. Hamilton, R. Bruning, H. Markowitsch, R. Kalla and M. Strupp, Spatial memory deficits and hippocampal atrophy in NF2 patients with bilateral vestibular failure, *J. Vestib. Res.* **14** (2004), 150.

[9] N. Chapuis, M. Krimm, C. de Waele, N. Vibert and A. Berthoz, Effect of post-training unilateral labyrinthectomy in a spatial orientation task by guinea pigs, *Behav. Brain Res.* **51** (1992), 115–126.

[10] H.S. Cohen, Vestibular disorders and impaired path integration along a linear trajectory, *J. Vestib. Res.* **10** (2000), 7–15.

[11] H.S. Cohen and K.T. Kimball, Improvements in path integration after vestibular rehabilitation, *J. Vestib. Res.* **12** (2002), 47–51.

[12] I.S. Curthoys and G.M. Halmagyi, Vestibular compensation: A review of the ocular motor, neural and clinical consequences of unilateral vestibular loss, *J. Vestib. Res.* **5** (1995), 67–107.

[13] I.S. Curthoys and G.M. Halmagyi, Vestibular compensation, *Advances Otorhinolaryngol.* **55** (1999), 82–110.

[14] P.C. Cuthbert, D.P. Gilchrist, S.L. Hicks, H.G. MacDougall and I.S. Curthoys, Electrophysiological evidence for vestibular activation of the guinea pig hippocampus, *Neuroreport* **11** (2000), 1443–1447.

[15] C.L. Darlington, P. Lawlor, P.F. Smith and M. Dragunow, Temporal relationship between the expression of Fos, Jun and Krox-24 in the guinea pig vestibular nuclei during the development of vestibular compensation for unilateral vestibular deafferentation, *Brain Res.* **735** (1996), 173–176.

[16] C. De Waele, P.M. Baudonniere, J.C. Lepecq, P. Tran Ba Huy and P.P. Vidal, Vestibular projections in the human cortex, *Exp. Brain Res.* **141** (2001), 541–551.

[17] S. Eagger, L.M. Luxon, R.A. Davies, A. Coelho and M.A. Ron, Psychiatric morbidity in patients with peripheral vestibular disorder: a clinical and neuro-otological study, *J Neurol Neurosurg Psychiat.* **55** (1992), 383–387.

[18] A.S. Etienne and K.J. Jeffery, Path integration in mammals, *Hippocampus.* **14** (2004), 180–192.

[19] J.M. Furman and R.G. Jacob, A clinical taxonomy of dizziness and anxiety in the otoneurological setting, *J. Anxiety Dis.* **15** (2001), 9–26.

[20] K. Fukushima, Corticovestibular interactions: anatomy, electrophysiology and functional considerations, *Exp. Brain Res.* **117** (1997), 1–16.

[21] V.V. Gavrilov, S.I. Wiener and A. Berthoz, Enhanced hippocampal theta EEG during whole body rotations in awake restrained rats, *Neurosci. Letts.* **197** (1995), 239–241.

[22] V.V. Gavrilov, S.I. Wiener and A. Berthoz, Whole-body rotations enhance hippocampal theta rhythmic slow activity in awake rats passively transported on a mobile robot, *Ann. NY Acad. Sci.* **781** (1996), 385–398.

[23] M. Gizzi, M. Zlotnick, K. Cicerone and E. Riley, Vestibular disease and cognitive dysfunction: no evidence for a causal connection, *J Head Trauma Rehabil.* **18** (2003), 398–407.

[24] C. Gliddon, C.L. Darlington and P.F. Smith, Activation of the hypothalamic-pituitary-adrenal axis in the guinea pig following unilateral labyrinthectomy, *Brain Res.* **964** (2003), 306–310.

[25] F. Godemann, M. Linden, P. Neu, E. Heipp and P. Dorr, A prospective study on the course of anxiety after vestibular neuronitis, *J. Psychosomatic Res.* **56** (2004), 351–354.

[26] J.A. Gray and N. McNaughton, *The Neuropsychology Of Anxiety: An Enquiry Into The Functions Of The Septohippocampal System*, (2nd Ed.), Oxford University Press, 2000.

[27] R.J. Grimm, W.G. Hemenway, P.R. Lebray and F.O. Black, The perilymph fistula syndrome defined in mild head trauma, *Acta Otolaryngol.* (*Stockh.*) **464**(Suppl.) (1989), 1–40.

[28] S.L. Hicks, D.P.D. Gilchrist, P. Cuthbert and I.S. Curthoys, Hippocampal field responses to direct electrical stimulation of the vestibular system in awake or anesthetised guinea pigs, *Proceedings of the Australian Neuroscience Society* **15** (2004), 87.

[29] A.J. Hill and P.J. Best, Effects of deafness and blindness on the spatial correlates of hippocampal unit activity in the rat, *Exp. Neurol.* **74** (1981), 204–217.

[30] A. Horii, N. Russell, P.F. Smith, C.L. Darlington and D. Bilkey, Vestibular influences on CA1 neurons in the rat hippocampus: an electrophysiological study in vivo, *Exp. Brain Res.* **155** (2004), 245–250.

[31] A. Horii, N. Takeda, T. Mochizuki, K. Okakura-Mochizuki, Y. Yamamoto and A. Yamatodani, Effects of vestibular stimulation on acetylcholine release from rat hippocampus: an in vivo microdialysis study, *J. Neurophysiol.* **72** (1994), 605–611.

[32] A. Horii, N. Takeda, T. Mochizuki, K. Okakura-Mochizuki, Y. Yamamoto, A. Yamatodani and T. Kubo, Vestibular modulation of the septo-hippocampal cholinergic system of rats, *Acta Otolaryngol.* (*Stockh.*) **520** (1995), 395–398.

[33] A. Horii, N. Takeda, T.A. Yamatodani and T. Kubo, Vestibular influences on the histaminergic and cholinergic systems in the rat brain, *Ann. NY Acad. Sci.* **781** (1996), 633–634.

[34] K.M. Horn, J.R. DeWitt and H.C. Nielson, Behavioral assessment of sodium arsanilate induced vestibular dysfunction in rats, *Physiol. Psych.* **9** (1981), 371–378.

[35] M. Johansson, D. Akerlund, H.C. Larsen and G. Andersson, Randomized controlled trial of vestibular rehabilitation combined with cognitive-behavioral therapy for dizziness in older people, *Otolaryngol Head Neck Surg.* **125** (2001), 151–156.

[36] L. Lindsay, P. Liu, C. Gliddon, Y. Zheng, P.F. Smith and C.L. Darlington, Cytosolic glucocorticoid receptor expression in the rat vestibular nucleus and hippocampus following unilateral vestibular deafferentation, *Exp. Brain Res.*, in press.

[37] P. Liu, C. Gliddon, L. Lindsay, C.L. Darlington and P.F. Smith, Nitric oxide synthase and arginase expression changes in the rat perirhinal and entorhinal cortices following unilateral vestibular damage: A link to deficits in object recognition? *J. Vestib. Res.*, in press.

[38] P. Liu, J. King, Y. Zheng, C.L. Darlington and P.F. Smith, Nitric oxide synthase and arginase expression in the vestibular nucleus and hippocampus following unilateral vestibular deafferentation in the rat, *Brain Res.* **966** (2003), 19–25.

[39] P. Liu, J. King, Y. Zheng, C.L. Darlington and P.F. Smith, Long-term changes in hippocampal NMDA receptor subunits following peripheral vestibular damage, *Neurosci.* **117** (2003), 965–970.

[40] L. Lundin-Olsson, L. Nyberg and Y. Gustafson, Stops walking when talking as a predictor of falls in elderly people, *Lancet.* **349**(9052) (1 Mar. 1997), 617.

[41] K. Maclennan, P.F. Smith and C.L. Darlington, Adrenalectomy-induced neuronal degeneration, *Prog. Neurobiol.* **54** (1998), 481–498.

[42] B.L. Mathews, J.H. Ryu and C. Bockaneck, Vestibular contribution to spatial orientation. Evidence of vestibular navigation in an animal model, *Acta Otolaryngol.* (*Stockh.*) **468** (1989), 149–154.

[43] B.L. McNaughton, C.A. Barnes, J.L. Gerard, K. Gothard, M.W. Jung, J.J. Knierim, H. Kudrimoti, Y. Qin, W.E. Skaggs, M. Suster and K.L. Weaver, Deciphering the hippocampal polyglot: The hippocampus as a path integration system, *J. Exp. Biol.* **199** (1996), 173–185.

[44] B.L. McNaughton, L.L. Chen and E.J. Markus, Dead reckoning, landmark learning, and the sense of direction: A neurophysiological and computational hypothesis, *J. Cog. Neurosci.* **3** (1991), 190–202.

[45] S. Miller, M. Potegal and L. Abraham, Vestibular involvement in a passive transport and return task, *Physiol. Psychol.* **11** (1983), 1–10.

[46] T. Mochizuki, K. Okakura-Mochizuki, A. Horii, Y. Yamamoto and A. Yamatodani, Histaminergic modulation of hippocampal acetylcholine release in vivo, *J. Neurochem.* **62** (1994), 2275–2282.

[47] D.G. Mumby, Perspectives on object recognition memory following hippocampal damage: lessons from studies in rats, *Behav. Brain Res.* **15** (2001), 9–26.

[48] K.P. Ossenkopp and E.L. Hargreaves, Spatial learning in an enclosed eight-arm maze in rats with sodium arsinilate-induced labyrinthectomies, *Behav. Neur. Biol.* **59** (1993), 253–257.

[49] P. Peruch, L. Borel, F. Gaunet, G. Thinus-Blanc, J. Magnan and M. Lacour, Spatial performance of unilateral vestibular defective patients in nonvisual versus visual navigation, *J. Vestib. Res.* **9** (1999), 37–47.

[50] M. Potegal, Vestibular and neostriatal contributions to spatial orientation, in: *Spatial Abilities: Development and Physiological Foundation*, M. Potegal, ed., New York, Academic Press, 1982.

[51] M.S. Redfern, M.E. Talkowski, J.R. Jennings and J.M. Furman, Cognitive influences in postural control of patients with unilateral vestibular loss, *Gait and Posture.* **19** (2004), 105–114.

[52] J. Risey and W. Briner, Dyscalculia in patients with vertigo, *J Vestib Res.* **1** (1990–1991), 31–37.

[53] J. Rossier, C. Haeberli and F. Schenk, Auditory cues support place navigation in rats when associated with a visual cue, *Behav. Brain Res.* **117** (2000), 209–214.

[54] N. Russell, A. Horii, P.F. Smith, C.L. Darlington and D. Bilkey, Effects of bilateral vestibular deafferentation on radial arm maze performance, *J. Vestib. Res.* **13** (2003), 9–16.

[55] N. Russell, A. Horii, P.F. Smith, C.L. Darlington and D. Bilkey, The long-term effects of permanent vestibular lesions on hippocampal spatial firing, *J. Neurosci.* **23** (2003), 6490–6498.

[56] N. Russell, P. Liu, C.L. Darlington, D. Bilkey, A. Horii and P.F. Smith, Hippocampal theta rhythm has decreased power in rats with bilateral vestibular labyrinthectomies, *Int. J. Neurosci.* **109** (2001), 212.

[57] F. Schautzer, D. Hamilton, R. Kalla, M. Strupp and T. Brandt, Spatial memory deficits in patients with chronic bilateral vestibular failure, *Ann NY Acad Sci.* **1004** (2003), 316–324.

[58] B.M. Seemungal, M.A. Gresty and A.M. Bronstein, The endocrine system, vertigo and balance, *Curr. Opin. Neurol.* **14** (2001), 27–34.

[59] P.F. Smith, Vestibular-hippocampal interactions, *Hippocampus* **7** (1997), 465–471.

[60] P.F. Smith, A. Horii, N. Russell, D. Bilkey, Y. Zheng, P. Liu, D.S. Kerr and C.L. Darlington, The effects of vestibular damage on hippocampal function in rats, *Prog. Neurobiol.*, (submitted).

[61] R.W. Stackman, A.S. Clark and J.S. Taube, Hippocampal spatial representations require vestibular input, *Hippocampus* **12** (2002), 291–303.

[62] R.W. Stackman and A.M. Herbert, Rats with lesions of the vestibular system require a visual landmark for spatial navigation, *Behav. Brain Res.* **128** (2002), 27–40.

[63] R.W. Stackman and J.S. Taube, Firing properties of head direction cells in the rat anterior thalamic nucleus: dependence upon vestibular input, *J. Neurosci.* **17** (1997), 4349–4358.

[64] J.S. Taube, J.P. Goodridge, E.J. Golob, P.A. Dudchenko and R.W. Stackman, Processing the head direction signal: A review and commentary, *Brain Res. Bull.* **40** (1996), 477–486.

[65] E. Vitte, C. Derosier, Y. Caritu, A. Berthoz, D. Hasboun and D. Soulie, Activation of the hippocampal formation by vestibular stimulation: a functional magnetic resonance imaging study, *Exp. Brain Res.* **112** (1996), 523–526.

[66] D.G. Wallace, D.J. Hines, S.M. Pellis and I.Q. Whishaw, Vestibular information is required for dead reckoning in the rat, *J. Neurosci.* **15** (2002), 10009–10017.

[67] S.I. Wiener and A. Berthoz, Forebrain structures mediating the vestibular contribution during navigation, in: *Multisensory Control of Movement*, A. Berthoz, ed., Oxford University Press, Oxford, 1993, pp. 427–456.

[68] S.I. Wiener, V.A. Korshunov, R. Garcia and A. Berthoz, Inertial, substratal and landmark cue control of hippocampal CA1 place cell activity, *Eur. J. Neurosci.* **7** (1995), 2206–2219.

[69] L. Yardley, J. Burhneay, I. Nazareth and L. Luxon, Neuro-otological and psychiatric abnormalities in a community sample of people with dizziness: a blind, controlled investigation, *J. Neurol. Neurosurg. Psychiat.* **65** (1998), 679–684.

[70] L. Yardley, M. Gardner, A. Bronstein, R. Davies, D. Buckwell and L. Luxon, Interference between postural control and mental task performance in patients with vestibular disorder and

healthy controls, *J. Neurol. Neurosurg. Psychiat.* **71** (2001), 48–542.

[71] L. Yardley, D. Papo, A. Bronstein, M. Gresty, M. Gardner, N. Lavie and L. Luxon, Attentional demands of continuously monitoring orientation using vestibular information, *Neuropsychologia* **40** (2002), 373–383.

[72] L. Yardley and M.S. Redfern, Psychological factors influencing recovery from balance disorders, *J Anxiety Disord.* **15** (2001), 107–119.

[73] R. Zhang, P.F. Smith and C.L. Darlington, Immunocytochemical and stereological studies of the rat vestibular nucleus: Optimal research methods using glucocorticoid receptors as an example, *J. Neurosci. Meth.*, in press.

[74] Y. Zheng, I. Appleton, P.F. Smith and C.L. Darlington, Subregional variation in the effects of unilateral vestibular deafferentation on nitric oxide synthase activity and nitrite formation in the guinea pig hippocampus, *Neurosci. Res. Comm.* **27** (2000), 109–116.

[75] Y. Zheng, C.L. Darlington and P.F. Smith, Bilateral vestibular deafferentation impairs object recognition in rat, *NeuroReport* **15** (2004), 1913–1916.

[76] Y. Zheng, A. Horii, I. Appleton, C.L. Darlington and P.F. Smith, Damage to the vestibular inner ear causes long-term changes in neuronal nitric oxide synthase expression in the rat hippocampus, *Neurosci* **105** (2001), 1–5.

[77] Y. Zheng, D.S. Kerr, C.L. Darlington and P.F. Smith, Peripheral vestibular damage causes a lasting decrease in the electrical excitability of CA1 in hippocampal slices in vitro, *Hippocampus* **13** (2003), 873–878.

[78] Y. Zheng, P.F. Smith and C.L. Darlington, Temporal bone surgery causes a reduction in nitric oxide synthase activity in the ipsilateral guinea pig hippocampus, *Neurosci Letts.* **259** (1999), 130–132.

[79] Y. Zheng, P.F. Smith and C.L. Darlington, Noradrenaline and serotonin levels in the guinea pig hippocampus following unilateral vestibular deafferentation, *Brain Res.* **836** (1999), 199–202.

[80] Y. Zheng, P.F. Smith and C.L. Darlington, Subregional analysis of amino acid levels in the guinea pig hippocampus following unilateral vestibular deafferentation, *J. Vestib. Res.* **10** (1999), 335–345.