Abstract

Vestibular dysfunction is associated with visual short-term memory impairment, however, it remains unclear if this impairment arises as a direct result of the vestibular dysfunction or is a consequence of comorbid changes in mood, affect, fatigue and/or sleep. To this end, we assessed the concurrence and inter-dependence of these comorbidities in 101 individuals recruited from a tertiary balance clinic with a neuro-otological diagnosis. Over fifty percent of the sample showed reduced visuospatial short-term memory, 60% and 37% exceeded cut-off on the Beck Anxiety and Depression Inventories respectively, 70% exceeded cut-off on the Fatigue Severity Scale, 44% reported daytime sleepiness on the Epworth Sleepiness Scale, and 78% scored above cut-off on the Pittsburg Sleep Quality Index. The high concurrence of these symptoms give reason to infer the existence of a vestibular cognitive affective syndrome. Structural equation modeling indicated that the significant statistical association between general unassisted posture (a marker of chronic vestibular dysfunction and strong predictor of falls risk) and short-term memory was not mediated by mood and wakefulness. Instead, the memory impairment related more directly to vestibular dysfunction. From a rehabilitation perspective, the implication is that if the vestibular disorder is treated successfully then the memory problem will likewise improve.

Keywords: Vestibular Disorders, Short-term Memory, Anxiety, Sleep, Fatigue.

Introduction

The vestibular system provides a constant stream of information about the orientation and movement of the head. This supports a variety of autonomic, multi-sensory functions including balance, posture, gait and, as we are increasingly becoming aware, higher brain function. The vestibular system is 'invisible' to conscious awareness until impacted by disease or injury at which point dizziness, a sensation of imbalance, nausea, and disorientation can appear. Beyond these acute effects, alterations in cognition and affect along with somnipathy and fatigue can persist for months to years (Best, Eckhardt-Henn, Tschan & Dieterich, 2009; Eagger, Luxon, Davies, Coelho & Ron, 1992; Tschan et al., 2011). The concurrence and inter-dependence of these comorbidities is not well understood, and there is particular uncertainty as to whether the cognitive symptoms are a consequence of these other comorbidities or whether they can arise independently (Bigelow & Agrawal, 2015; Hanes & McCollum, 2006). These ambiguities, which form the focus of the current study, have made it difficult to determine both the functional specificity of the ascending vestibular afferents and how best to manage cognitive impairment in vestibular patients.

The cognitive impairments that accompany balance disorder are varied although most commonly apparent in spatial tasks, most notably those involving memory and navigation. Attentional tasks of a less spatial nature involving word retrieval, perceptual discrimination, dual processing and event sequencing (Black, Pesznecker & Stallings, 2004) can also be affected (for recent reviews see Bigelow and Agrawal, 2015; Gurvich et al., 2013; Smith and Darlington, 2013). Detailed prevalence studies are few but according to the 2008 US National Health Survey, individuals with self-reported balance symptoms have an eight-fold increased odds of self-perceived difficulty in concentrating or remembering compared to the adult population (Bigelow, Semenov, du Lac, Hoffman & Agrawal, 2015).

The main psychiatric symptoms reported after the onset of a balance disorder, especially in individuals with vestibular migraine (Lahmann et al., 2014) or Menière's Disease (Eckhardt-Henn et al., 2008), are generalised anxiety, major depression, panic attacks, agoraphobia and depersonalisation. Reported prevalence has exceeded 50% - three times greater than in the general population - with symptoms often persisting after the vestibular disturbance has been treated (Guidetti, Monzani, Trebbi & Rovatti, 2008). Some studies that have used different participant inclusion criteria and outcome measures have however reported lower rates (Grunfeld, Gresty & Bronstein, 2003; Ketola, Havia, Appelberg & Kentala, 2007). Accurate estimates are also hampered because common outcome assessments, many of which are non-standardised, have not been applied. Many patients also report disturbed sleep and significant fatigue although only a few studies have investigated these complaints; Eagger et al. (1992) showed that fatigue, along with depression, was the most commonly reported symptom 3-5years after initial referral for a peripheral vestibular disorder, while Yardley et al. (1998) noted that 85% of dizzy patients recruited to her sample from general practice experienced fatigue symptoms, relative to 33% of neurologically healthy controls. More recently, Salhofer et al. (2010) compared the sleep quality of patients with vestibular and non-vestibular migraine and found those with migraine trended towards having poorer sleep.

Although the coincidence of comorbid neuropsychiatric impairment in individuals with balance problems has not yet been assessed within a single sample, there is enough evidence to indicate that it is likely to be high. If true then this could be taken to suggest that cognitive deficits arise as a consequence of these other comorbidities. In broad support of such an idea, the deleterious effects of anxiety and depression on demotivation and distractibility (Capuron et al., 2006; Eysenck, Derakshan, Santos & Calvo, 2007; Neu et al., 2011), and thereon cognitive performance are well-established within general practice. In addition to the negative psychological response to feeling dizzy and unsteady, psychiatric symptoms may emerge more

directly by virtue of the dense neuronal connectivity between the ascending vestibular brainstem fibres and the limbic and arousal systems. Balaban, Jacob and Furman (2011) identify shared organisational and neurochemical features across these systems that enable dysfunction within one to be propagated across the others. Some of these areas, notably the insula, hippocampus, and prefrontal / cingulate cortices are also directly implicated in cognitive function so provide a common substrate through which vestibular-affective disturbance could cause cognitive impairment (Smith & Zheng, 2013). In line with this idea, a recent study (Bigelow et al., 2015) showed that the presence of executive and memory impairment in those reporting balance symptoms was significantly mediated by depression, anxiety and panic disorder which together accounted for 32% of the variance. As highlighted by the authors, however, this study relied on a small number of 'self-reported outcomes without any objective assessment of vertigo, depression or cognition' (Bigelow et al., 2015, p.5) so may have missed vestibular sub-groups and cognitive outcomes that do support a more direct relationship.

Although comorbid disorders may partly elicit the cognitive symptoms seen in vestibular patients, evidence suggests that the vestibular pathology may make a more specific contribution to cognitive functioning. Anecdotally, practitioners involved in vestibular rehabilitation speak to an 'orientation first' principle in which attentional resources usually devoted to cognition are recruited to support balance function when the vestibular system becomes compromised and cannot do this automatically (Ayres, 1978; Redfern, Talkowski, Jennings, & Furman, 2004). In line with this notion, dual-task studies demonstrate that patients with vestibular dysfunction perform more poorly on information processing tasks when in a posturally challenging environment (see Bigelow & Agrawal, 2015 and Hanes & McCollum, 2006, for reviews). At a theoretical level, computational models posit that vestibular signals underpin the formation of multi-sensory spatial reference frames in the temporal and parietal lobes that are necessary for self-motion perception and navigation (e.g. Hitier, Besnard &

Smith, 2014; Karnath & Dieterich, 2006; Vallar, 1997). This assertion rests strongly on the twin findings that (i) peripheral vestibular dysfunction is associated with atrophy within hippocampal head position and place cells, and (ii) deficits in spatial memory and navigation are common in vestibular patients (Dieterich & Brandt, 2008; Kremmyda et al., 2016; Yoder & Taube, 2009; Ventre-Dominey, 2014). Another line of evidence shows that artificial stimulation of the vestibular labyrinth via thermal or electric current can improve a variety of perceptual and memory behaviours following neurological disease (e.g. Wilkinson et al., 2014; Wilkinson, Podlewska & Sakel, 2016), an effect that is consistent with the broad peri-sylvian activity observed during stimulation (see Lopez, 2016).

In light of the above uncertainty around the prevalence and inter-dependency of cognitive (specifically spatial memory and information processing), psychiatric and sleep/fatigue disturbances in individuals with vestibular disorder, the aim of the present study was to obtain improved estimates by administering, within a single sample, broader and more standardised range of assessments than before. Structural equation modelling was applied to help establish if short-term memory is affected by vestibular dysfunction independently of psychiatric and sleep/fatigue disturbances.

Material and methods

Participants

101 participants were recruited from a Neuro-otology / Balance Centre service over a 12month period (see Table 1). Patients were offered the opportunity to undergo eligibility screening when arriving at their initial appointment which had been arranged following a referral for complaints of dizziness, vertigo and/or unsteadiness. On average, participants had waited 2years from initial GP consultation before being referred to the balance centre. During

eligibility screening, unsteadiness, light headedness, vertigo, visual dominance/ sensitivity and nausea were the most commonly reported symptoms. Most patients reported a constant balance problem (73%), and most reported acute attacks in which their symptoms became much worse (72%). Only 3% reported feeling normal in between acute attacks.

Ethics approval was obtained prior to study from the East of England (Cambridge) Research Ethics Committee (REC No. 14/EE/1041).

Study inclusion criteria:

- Diagnosis of vestibular disorder made by a consultant neuro-otologist based on, where appropriate: International Classification of Headache Disorders (ICHD-2) (Olesen & Steiner, 2014), International Classification of Disease 10th Revision (ICD-10) (World Health Organisation, 1992), Consensus Document of the Barany Society and the International Headache Society (for vestibular migraine) (Lempert et al., 2012), and head positioning tests.

Study exclusion criteria:

- Comorbid cardio-vascular symptoms that could also cause syncopal light-headed type dizziness.
- Premorbid history of traumatic brain injury.
- Premorbid history of a neurological or psychiatric condition for which a referral to secondary care was made.

Assessments

Neuro-otological. All examinations were carried out by a consultant neuro-otologist and comprised a detailed history and neuro-otological examination. Additional balance function assessment included video-nystagmography (VNG), and video-Head Impulse Testing (vHIT). Balance platform testing was also performed in which participants had to maintain their balance

for 30s under four test conditions which varied, by means of eyes open/closed and the stability of the surface (foam vs firm), the degree to which visual, proprioceptive and vestibular cues could be used. The most difficult condition (eyes closed, foam surface) relied almost exclusively on the use of vestibular inputs. These largely objective measures were supplemented by three self-report questionnaires: the Vertigo Symptom Scale- VSS (Yardley, Masson, Verschuur, Haacke & Luxon, 1992), the Dizziness Handicap Inventory- DHI (Jacobson & Newman, 1990), and the Visual Vertigo Analogue Scale- VAS (Longridge, Mallinson & Denton, 2002). The VNG and vHIT were scored categorically (abnormal/ normal) and the balance platform was analysed in terms of velocity of sway in millimetres per second.

Psychiatric. Standardised assessments with clinical norms were administered in a single session to assess depression (Beck Depression Inventory- BDI (Beck, Steer & Brown, 1993)), anxiety (Beck Anxiety Inventory- BAI (Beck & Steer, 1993)), depersonalisation (Cambridge Depersonalisation Scale- CDS (Sierra & Berrios, 2000)), fatigue (Fatigue Severity Scale- FSS (Krupp, LaRocca, Muir-Nash & Steinberg, 1989)), and sleepiness (Epworth Sleepiness Scale- ESS (Johns, 1991) and Pittsburg Sleep Quality Index- PSQI (Buysse, Reynolds, Monk, Berman & Kupfer, 1989)).

Cognitive. A battery of six computer-interfaced tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins & Sahakian, 1994) was administered. Based on reports that the most common vestibular-related impairments involve spatial memory and information processing (Smith & Darlington, 2013), the following tests were used: delayed match to sample (DMS), paired associates learning (PAL), spatial working memory (SWM), spatial span (SSP), reaction time (RTI) and rapid visual processing (RVP).

Each of these tests placed different emphases on the need for spatial versus non-spatial processing and executive planning (for further details see Table 4 in the supplementary text).

Procedure

Following written informed consent, all participants were neuro-otologically assessed, after which they completed psychiatric and cognitive measures in a clinic side room. To counterbalance any order effects the cognitive tests were administered in the order PAL, RVP, SWM, RTI, SSP, DMS in one half of the participants, with the other half receiving the tests in reverse order. Tests were carried out on standard display tablets supplied by CANTAB (Gigabyte^{TM} S10). The questionnaires were administered in random order. The complete assessment procedure took approximately two hours.

Results

Statistical approach

The prevalence of neuropsychiatric impairment was first obtained by comparing participants' test scores to established clinical cut-offs (psychiatric/ fatigue questionnaires) and age-matched normed data (cognitive outcome measures). The factorability and underlying components of the principal CANTAB outcome measures was then examined. Once the model structure had been confirmed, a series of mediation models were constructed using SEM in AMOS^{TM} 23 which can combine confirmatory factor analysis with multiple regression. In addition to the details provided below, further information about the SEM procedure is reported in the supplementary text.

Prevalence of psychiatric and cognitive symptoms

The cognitive assessments showed widespread age- and gender-matched impairment (i.e. the participant obtained a negative z score indicating lower performance than the normative mean, see Table 2). Psychiatric symptoms were also widespread (see Figure 1). 60% of

participants reported BAI scores above clinical cut-off and 37% fell above the clinical cut-off for depression. Over 70% of the sample exceeded clinical cut-off for fatigue and 44% reported significant daytime sleepiness on the ESS. 78% exceeded the cut-off on the PSQI. By contrast, the incidence of depersonalisation disorder was low (13%).

Core cognitive components

Correlation analyses first showed the majority of the cognitive measures shared significant moderate associations suggesting the data were suitable for factor analysis (see Table 5 supplementary text). In line with other studies, the two time-based measures (Simple RTI ms and RVP ms) were treated separately. An exploratory factor analysis (EFA) with Maximum Likelihood extraction and Promax rotation (performed in IBM SPSS Statistics 23) was therefore completed to investigate the factor structure underpinning the other seven measures (RTI accuracy, RVP d', SSP, PAL %correct, DMS, SWM %correct). Reaction times for the two attention-based tasks (RTI and RVP) were averaged into a single index ('processing speed') and were analysed as a separate variable (EFA cannot be completed upon two outcome measures).

Ninety seven percent of participants provided a complete set of data on these outcome measures and were therefore included in the analysis. The EFA identified a single factor that explained 32% of variance within the accuracy-based cognitive outcome measures. Marker items included the PAL (%correct) and SWM (%correct) which led us to term the factor 'visuospatial memory'. Confirmatory factor analysis (CFA) performed in AMOS™ using Maximum Likelihood extraction showed that this measurement model was a good fit to the observed data according to the fit indices (Comparative fit index (CFI)= 1.00; Root mean square error of approximation (RMSEA)= 0.00; χ^2 (13, N= 98)= 10.59, p= .65) and

standardised residuals (all <1.96) (Byrne, 2010; Hooper, Coughlan & Mullen, 2008). Factor loadings were all high (>0.31) and significantly different from zero (see Table 6 supplementary text).

Mediation analyses

The above cognitive components (visuospatial memory and processing speed) were then implemented within full SEM to test causal mediation hypotheses. Of the 101 participants, 95 provided a complete set of data on all the outcome measures utilised in these more complex models.

Mediation analyses first confirmed that vestibular dysfunction contributed to cognitive impairment (visuospatial memory and processing speed factors) over and above normal age-related changes. Only the model investigating performance on the balance platform (posturography) and visuospatial memory ability revealed a significant mediation (ß= -0.09, $p<.05$; all other indirect paths $p>.28$). Performance on the balance platform mediated 17% of the association between age and visuospatial memory such that older participants who showed increased sway also presented with poorer performance on the visuospatial memory factor (see Figure 3 in the supplementary text).

Global fit indices (CFI= 0.91; RMSEA= 0.099; $\chi^2(51, N= 95)= 99.34$, $p<.001$) and standardised model residuals (only two coefficients >1.96) suggested adequate fit between the model and observed data. Importantly, because the measurement models for both the visuospatial memory and balance platform factors indicated good fit to the data, any areas of misfit were likely due to fact that only a few paths had been omitted within these SEMs (see Tables 6 and 7 in the supplementary text).

The next analysis aimed to determine the fraction of the association between balance function and visuospatial memory that could be explained by comorbid psychiatric, sleep and

fatigue symptoms (having first accounted for any age-related change). If cognitive impairments in this cohort arise as a secondary consequence of these co-morbid disturbances, then the indirect path within the mediation analysis should reach significance.

Two combinations of mediators were applied. The first examined the influence of psychiatric variables on visuospatial memory including the BDI, BAI and VSS_SA (Vertigo Symptom Scale-Somatic Anxiety). The VSS_SA was treated as a mediator in this model because the symptomology assessed by this scale is strongly associated with anxiety, and reflect patients' psychiatric and somatic responses to the balance problem (Yardley et al., 1992). A second model estimated whether the presence of fatigue and sleep disturbance exerted an indirect influence on visuospatial memory using the FSS, ESS and PQI. As these comorbid measures all involved self-reported perceptions of wellbeing for which no prior predictions were held about their independence, covariance paths were drawn between the three test residuals in each model.

Nested models were fit and compared for each combination of mediators (see Figures 2A and 2B). The first model tested the strength of the indirect paths involving the mediators (psychiatric or sleep/fatigue) to establish whether a significant association was present. A second model then added the direct path to evaluate the strength of the indirect relationship once the direct path between the balance platform and visuospatial memory had been controlled for. Four models were fitted and tested, all adjusted for age.

Neither the indirect effect of the psychiatric nor the fatigue variables reached significance, regardless of whether the direct path was controlled for (all ßs<0.03, all ps>.50). Combined depression, anxiety and somatic anxiety only slightly suppressed the effect of posturography on visuospatial memory performance, reducing the total path by a negligible margin (direct ß= -0.27; total ß= -0.24). Likewise, the suppressive effect of fatigue severity,

sleepiness and sleep quality on the association between posturography and visuospatial memory was minimal (direct ß= -0.23; total ß= -0.22). Importantly, the negative direct path between the balance platform and performance on the visuospatial memory factor accounted for the majority of variance within the total path across both mediator models. Additionally, the direct path remained significant across the psychiatric mediators (ß= -0.27, $p<.05$) and fell on the cusp of significance for the fatigue mediators (ß= -0.23, $p=.05$).

Chi-square difference tests were used to compare the fit of these nested models once the direct path between the balance platform and visuospatial memory was added. If balance function only interacts with cognition indirectly then the additional path between balance function and visuospatial memory should not improve the fit. In line with the regression results above, Table 3 shows that the direct path significantly improved the fit of the model involving the psychiatric variables, while the effect narrowly missed significance within the fatigue model. Standardised model residuals similarly indicated better fit in the models which included the direct paths (one significant discrepancy for the path between RTI_acc and balance platform firm-eyes open for both psychiatric ß= -2.80 and fatigue ß= -2.76 models) compared to the more parsimonious models which did not (four and three significant residuals for the fatigue and psychiatric models respectively).

Discussion

Patients with vestibular dysfunction are often depressed, anxious, tired and have difficulty concentrating and remembering (Bigelow et al., 2015; Grimm, Hemenway, Lebray & Black, 1989; Lahman et al., 2014). We have shown in the cohort of patients studied here, most of whom have been diagnosed with vestibular migraine, that these co-morbidities frequently occur together. There are few existing prevalence estimates of memory impairment,

sleeplessness and fatigue, although the incidence of depression and anxiety seen here is slightly higher than that previously reported via alternative assessment (Eagger et al., 1992; Eckhardt-Henn et al., 2008; Lahmann et al., 2014). We also found that difficulties in short-term visuospatial memory are significantly and independently associated with performance on the balance platform test, a measure of unassisted posture especially sensitive to the chronic aspects of vestibular dysfunction and strongly associated with falls risk (Agrawal, Carey, Della Santina & Schuber, 2009). This finding suggests for the first time that aspects of balance play an important role in memory, irrespective of limbic or arousal influence.

The close relationship uncovered by the mediation analysis between vestibular and short-term memory processes is perhaps surprising because it is reliant on indirect anatomical connections. These connections are believed to take four main routes from the vestibular nucleus complex to the hippocampus, three of which are thalamo-cortical and pass through the cerebellum, parietal cortex and para-/post-subiculum respectively. The fourth route projects to the hippocampal complex via the supramamillary nucleus and medial septum (Hitier et al., 2014). According to Balaban and colleagues (2011), these ascending pathways support a number of cognitive and interoceptive functions, sharing serotonergic and nor-adrenergic inputs from vestibular-dorsal raphe nucleus and vestibular-coeruleus pathways. These ascending pathways provide a substrate through which vestibular disorder can cause memory impairment. Although the correlational basis of mediation analysis prevents attribution about whether, in our study participants, the vestibular deficit caused the memory problem, support for such an idea can be taken from the fact that participants only began to report memory impairment after their vestibular symptoms took hold. In line with this self-report, participants' referral notes did not highlight pre-existing memory problems, and our study exclusion criteria out-ruled individuals with a prior neurological or psychiatric history that, inter alia, included amnesic episodes. Coupled with the fact that we cannot find report of individuals with amnesia

who have later developed vestibular problems, we suggest that the memory impairments observed here were much more likely caused by the vestibular disorder than vice-versa. The role of a third, uncontrolled deficit that induced impairment in both systems and yet affected limbic and sleep processes to a lesser degree and did not induce other neurological and psychiatric signs, cannot be dismissed. However, the clinical literature makes no mention of any such deficit.

One unresolved issue underlined by the wide profile of observed neuropsychiatric impairment concerns the informational content that memorial and affective processes draw from the vestibular afference. Rat studies indicate that the momentary changes in angular and linear acceleration of the head signalled by the vestibular organs modulate the activity of hippocampal place and head direction cells (and maybe also grid cells) relevant to the formation of cognitive maps and spatial memories (Hitier et al., 2014). But quite which elements of the vestibular signal are important for arousal and, perhaps more challengingly, feelings of well-being remain unclear. As indicated by the sea- and cyber-sickness that can occur during vestibular-visual mismatch, predictability and congruence with other sensory inputs are probably more important than the spatial properties of the movement vector itself. But given the dense connections between vestibular brainstem nuclei and vestibular parieto-insular cortex with autonomic, interoceptive and limbic centres (see Lopez, 2016), the possible means of influence are many and varied. Such complexity highlights the pressing need for an over-arching conceptual framework within which to explore vestibular cross-modal interactions.

From a clinical perspective, we note that the presence of underlying vestibular disorder is not always easy to diagnose, a fact underlined by the fact that in the UK dizzy/unsteady patients are usually referred to a neurologist and ENT specialist before seeing a neuro-otologist. Given the high concurrence of cognitive, psychiatric and sleep symptoms – which we suggest

amounts to a ‘vestibular cognitive affective’ syndrome – there may be utility in developing a brief neuropsychological screen that measures short-term memory capacity, depression, anxiety, fatigue and sleep to help primary care physicians determine the merit of an initial neuro-otological referral. Referring patients to a psychiatrist, as sometimes occurs, with the expectation that the cognitive symptoms will recede once the affective symptoms are brought under control will not necessarily be successful given the findings of this study. In fact, prescribed medications for these ailments such as SSRI anti-depressants (e.g. citalopram), benzodiazepines and hypnotics are known to further suppress cognition (Ramos, 2006) so could be counter-productive. What these patients need, first and foremost, is the accurate diagnosis and adequate treatment of the root cause of all their symptoms - the balance disorder - after which many of the neuropsychiatric problems will also likely resolve.

The relevance of vestibular dysfunction to neuropsychiatric practice has taken much time to gain prominence. Our understanding of the role of the peripheral vestibular end organs began with the work of Flourens in the 19th century, and progressed with the elucidation of vestibular brainstem nuclei function in the 19th and 20th centuries (Duque-Parra, 2004). However, it is only in the last few decades that the role of the cerebral cortex and subcortical structures in vestibular function has begun to be appreciated. It is now apparent that there are widespread vestibular projections to many multi-sensory cortical areas, as well as reciprocal corticofugal projections to the brainstem. Much remains to be understood about the ‘vestibular cognition’ that emerges from these networks, and to this end the current data demonstrate extensive interactions between the vestibular afference and processes involved in affect, sleep, wakefulness and cognition. Although these processes are jointly compromised by vestibular dysfunction, the effects on visuospatial memory appear to occur independently. This evidence of modularised effect counters the idea that the diffuse and multi-sensory qualities of the vestibular system only shape mood and cognition in a domain-general manner. Future research

will need to determine the inter-dependency of the other comorbidities reported here. Resources permitting, it would also be informative to adopt a longitudinal design to track the relative time-course of symptoms, to recruit larger samples to model the effects of additional demographic and clinical characteristics, and to more thoroughly assess the cognitive and affective impairments described here. In the meantime, we propose that the case for initial neuro-otological referral should take greater account of the concurrence of neuropsychiatric symptoms, with subsequent treatment recognising the common origin of the seemingly disparate, multi-faceted symptoms of vestibular dysfunction.

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Table 1. Participant demographics

Diagnosis	N	%	Age		Gender		Constantly Presenting	
			M	SD	Male	Female	Yes	No
VM*	64	63.4	43.9	14.1	13	51	47	17
BPPV	8	7.9	59.5	11.4	1	7	5	3
BVF/ hypofunction	3	3	58.7	5.1	1	2	3	0
VM & BPPV	7	6.9	53.6	8.5	0	7	4	3
VM & peripheral loss	6	5.9	46.5	15.1	3	3	6	0
MD	2	2	54.5	12.2	1	1	1	1
Central dysfunction	5	5	60.9	7.3	3	2	5	0
C & P hypofunction	1	1	68.3	-	0	1	1	0
Other	5	5	54.4	14.3	2	3	4	1
Total	101	100	48.2	14.3	24	77	76	25

* VM= vestibular migraine; BPPV= benign paroxysmal positional vertigo; BVF= bilateral vestibular failure; MD= Meniere's disease; C & P= central and peripheral.

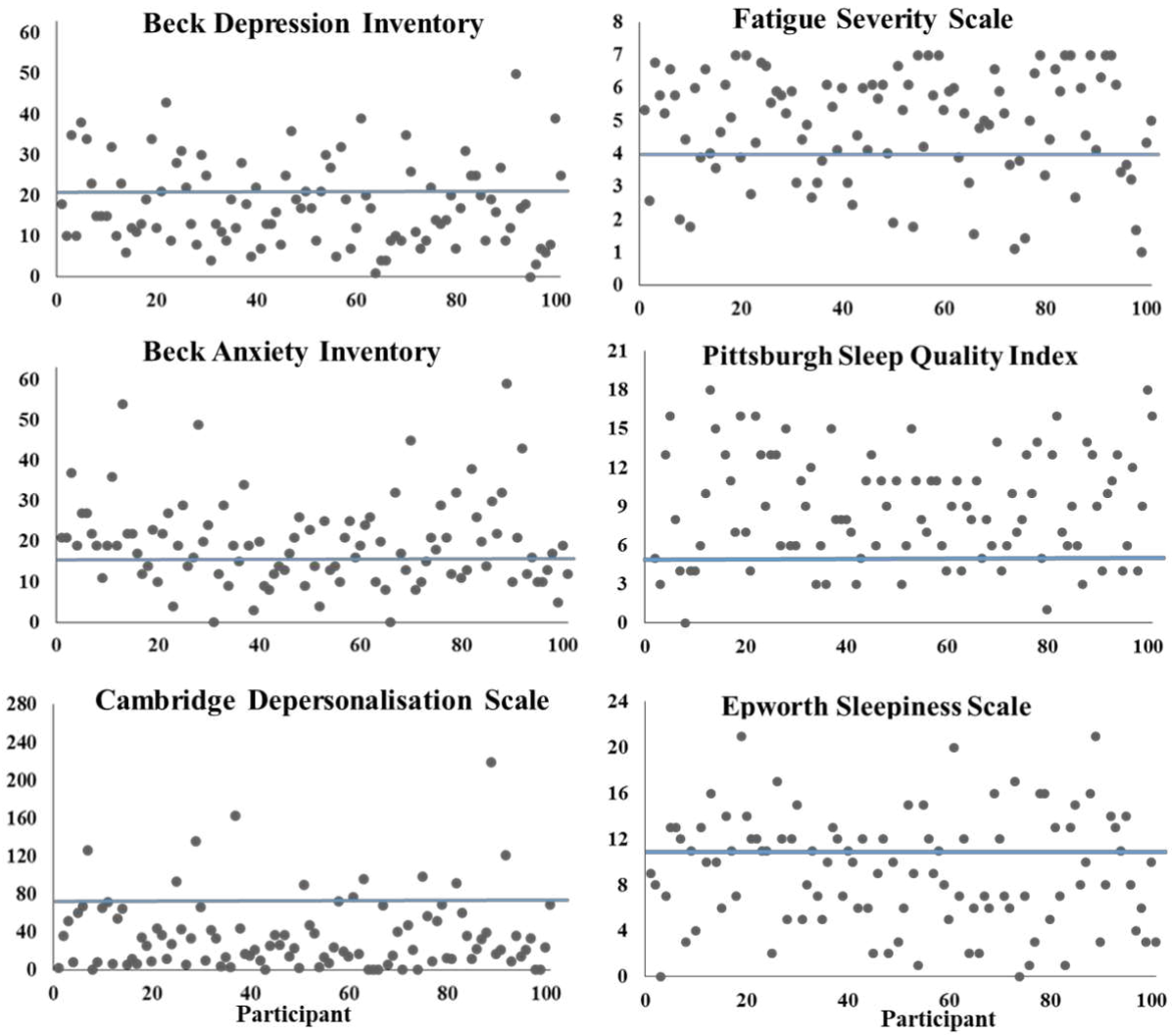

Figure 1. Relative incidence (%) of psychiatric and fatigue/sleep morbidities across the 101 participants. Horizontal lines show established clinical cut-offs.

Table 2. Descriptive statistics and relative incidence (%) of cognitive morbidity, as measured by each of the normed CANTAB subtests

CANTAB Subtest	**Mean**	**SD**	**% falling outside cut-off**
Delayed match to sample (DMS)	81.2	12.7	51
Paired associates learning errors (PAL)	24.7	32.3	29
Spatial working memory errors (SWM_E)	33.1	21.5	50
Spatial working memory strategy (SWM_S)	33.6	8.3	53
Spatial span (SSP)	5.8	1.3	56
Reaction time (RTI) (msecs)	343	84	44
Rapid visual processing *d'* (RVP)	0.88	0.55	63
Rapid visual processing RVP (msecs)	456	148	24

Note. Raw descriptive statistics are presented alongside the percentages of participants that fell below normative performance limits. Where possible, participants' performance was matched with the normative sample in terms of age and gender. SD=standard deviation.

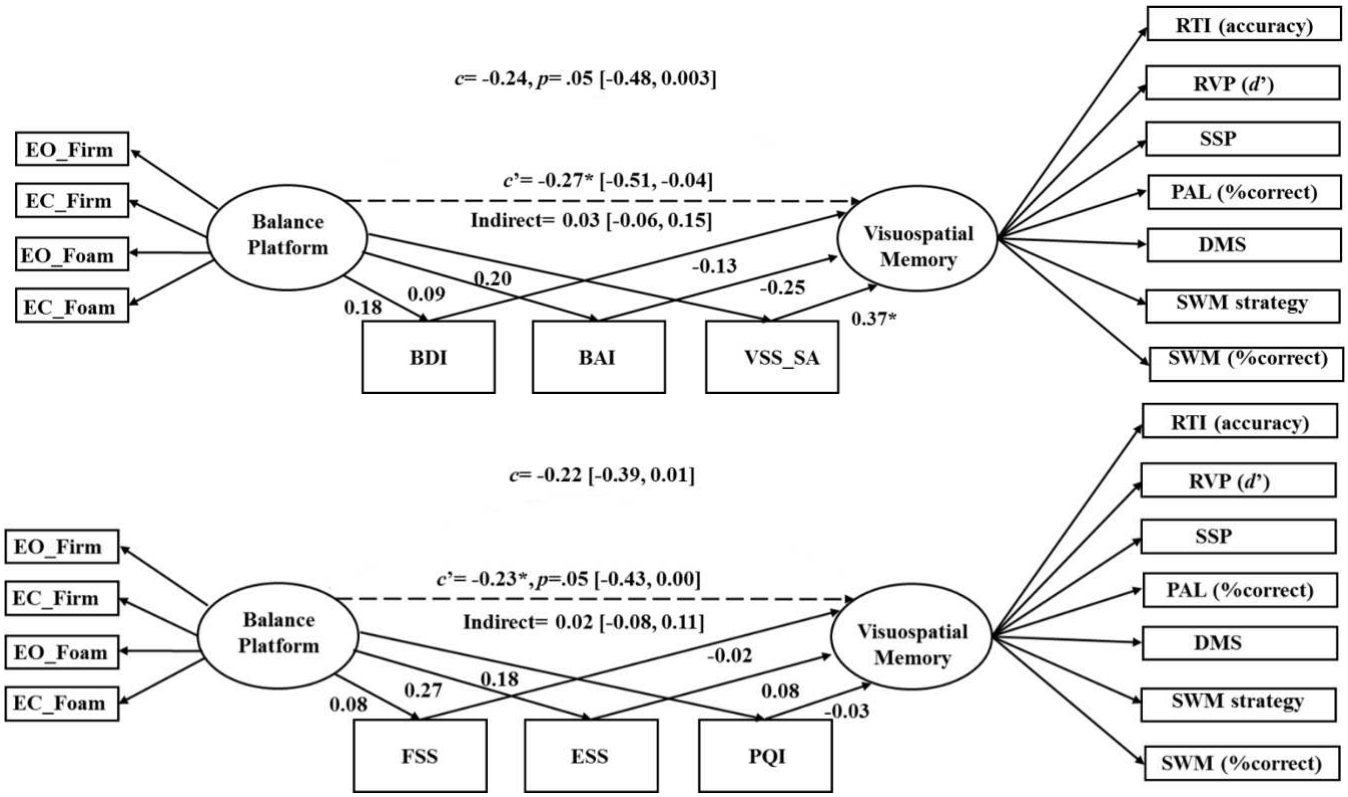

Figure 2. Mediation models for the psychiatric (A) and fatigue (B) variables with direct paths (dashed lines).

* Standardised coefficients are reported alongside bias-corrected 95% confidence intervals and significance values, *p<.05, **p<.01. All 95% CIs were derived from bootstrapping estimations after 2,000 simulations. Errors from the SWM strategy and SWM (%correct) indicators were allowed to correlate to account for method effects, as well as errors from the self-report questionnaires. Latent factors utilised the scale of the most conceptually relevant observed variable in accordance with the factor loadings. All results were adjusted for age.

Table 3. Chi-square difference (χ^2) tests between mediation models which freely estimated or controlled for the direct pathway between posturography and visuospatial memory

Model	**Estimates of Fit**	**χ^2 Difference tests**
Psychiatric Indirect	$\chi^2(79, N = 95) = 125.08$, p= .001 CFI= .92 RMSEA= .08	125.08 - 120.08 = 5. The addition of the direct path significantly improved model fit (>3.841 critical χ^2 difference for 1 df).
Psychiatric Indirect & Direct	$\chi^2(78, N = 95) = 120.08$, p= .002 CFI= .93 RMSEA= .08	
Fatigue Indirect	$\chi^2(79, N = 95) = 140.35$, p<.001 CFI= .89 RMSEA= .09	140.35 – 136.90 = 3.45. The addition of the direct path did not significantly improve model fit (<3.841 critical χ^2 difference for 1 df).
Fatigue Indirect & Direct	$\chi^2(78, N = 95) = 136.90$, p<.001 CFI= .90 RMSEA= .09	

Note. Chi-square difference (χ^2) tests were calculated using the formula: χ^2 diff = χ^2S − χ^2L and df diff = dfS – dfL, where "S" denotes the smaller model with fewer parameters to estimate and therefore more degrees of freedom, whereas "L" denotes the larger model with more parameters and therefore fewer degrees of freedom. This χ^2 diff-value is distributed with dfdiff degrees of freedom and can be checked manually for significance using a χ^2 table (Werner & Schermelleh-Engel, 2010).