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1 **Abstract**

2 Vestibular dysfunction is associated with visual short-term memory impairment, however, it
3 remains unclear if this impairment arises as a direct result of the vestibular dysfunction or is a
4 consequence of comorbid changes in mood, affect, fatigue and/or sleep. To this end, we
5 assessed the concurrence and inter-dependence of these comorbidities in 101 individuals
6 recruited from a tertiary balance clinic with a neuro-otological diagnosis. Over fifty percent of
7 the sample showed reduced visuospatial short-term memory, 60% and 37% exceeded cut-off
8 on the Beck Anxiety and Depression Inventories respectively, 70% exceeded cut-off on the
9 Fatigue Severity Scale, 44% reported daytime sleepiness on the Epworth Sleepiness Scale, and
10 78% scored above cut-off on the Pittsburg Sleep Quality Index. The high concurrence of these
11 symptoms give reason to infer the existence of a vestibular cognitive affective syndrome.
12 Structural equation modeling indicated that the significant statistical association between
13 general unassisted posture (a marker of chronic vestibular dysfunction and strong predictor of
14 falls risk) and short-term memory was not mediated by mood and wakefulness. Instead, the
15 memory impairment related more directly to vestibular dysfunction. From a rehabilitation
16 perspective, the implication is that if the vestibular disorder is treated successfully then the
17 memory problem will likewise improve.

18

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

20

21

22 **Introduction**

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

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

46 The main psychiatric symptoms reported after the onset of a balance disorder,
47 especially in individuals with vestibular migraine (Lahmann et al., 2014) or Menière's Disease
48 (Eckhardt-Henn et al., 2008), are generalised anxiety, major depression, panic attacks,
49 agoraphobia and depersonalisation. Reported prevalence has exceeded 50% - three times
50 greater than in the general population - with symptoms often persisting after the vestibular
51 disturbance has been treated (Guidetti, Monzani, Trebbi & Rovatti, 2008). Some studies that
52 have used different participant inclusion criteria and outcome measures have however reported
53 lower rates (Grunfeld, Gresty & Bronstein, 2003; Ketola, Havia, Appelberg & Kentala, 2007).
54 Accurate estimates are also hampered because common outcome assessments, many of which
55 are non-standardised, have not been applied. Many patients also report disturbed sleep and
56 significant fatigue although only a few studies have investigated these complaints; Eagger et
57 al. (1992) showed that fatigue, along with depression, was the most commonly reported
58 symptom 3-5years after initial referral for a peripheral vestibular disorder, while Yardley et al.
59 (1998) noted that 85% of dizzy patients recruited to her sample from general practice
60 experienced fatigue symptoms, relative to 33% of neurologically healthy controls. More
61 recently, Salhofer et al. (2010) compared the sleep quality of patients with vestibular and non-
62 vestibular migraine and found those with migraine trended towards having poorer sleep.

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

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

84 Although comorbid disorders may partly elicit the cognitive symptoms seen in
85 vestibular patients, evidence suggests that the vestibular pathology may make a more specific
86 contribution to cognitive functioning. Anecdotally, practitioners involved in vestibular
87 rehabilitation speak to an 'orientation first' principle in which attentional resources usually
88 devoted to cognition are recruited to support balance function when the vestibular system
89 becomes compromised and cannot do this automatically (Ayres, 1978; Redfern, Talkowski,
90 Jennings, & Furman, 2004). In line with this notion, dual-task studies demonstrate that patients
91 with vestibular dysfunction perform more poorly on information processing tasks when in a
92 posturally challenging environment (see Bigelow & Agrawal, 2015 and Hanes & McCollum,
93 2006, for reviews). At a theoretical level, computational models posit that vestibular signals
94 underpin the formation of multi-sensory spatial reference frames in the temporal and parietal
95 lobes that are necessary for self-motion perception and navigation (e.g. Hitier, Besnard &

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

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

112

113 **Material and methods**

114 **Participants**

115 101 participants were recruited from a Neuro-otology / Balance Centre service over a
116 12month period (see Table 1). Patients were offered the opportunity to undergo eligibility
117 screening when arriving at their initial appointment which had been arranged following a
118 referral for complaints of dizziness, vertigo and/or unsteadiness. On average, participants had
119 waited 2years from initial GP consultation before being referred to the balance centre. During

120 eligibility screening, unsteadiness, light headedness, vertigo, visual dominance/ sensitivity and
121 nausea were the most commonly reported symptoms. Most patients reported a constant balance
122 problem (73%), and most reported acute attacks in which their symptoms became much worse
123 (72%). Only 3% reported feeling normal in between acute attacks.

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

126

127 Study inclusion criteria:

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

134 Study exclusion criteria:

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

140 **Assessments**

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

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

154

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

162

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

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

171 **Procedure**

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

179 **Results**

180 **Statistical approach**

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

189 **Prevalence of psychiatric and cognitive symptoms**

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

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

197

198 **Core cognitive components**

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

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

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

220 **Mediation analyses**

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

225 Mediation analyses first confirmed that vestibular dysfunction contributed to cognitive
226 impairment (visuospatial memory and processing speed factors) over and above normal age-
227 related changes. Only the model investigating performance on the balance platform
228 (posturography) and visuospatial memory ability revealed a significant mediation ($\beta = -0.09$,
229 $p < .05$; all other indirect paths $p > .28$). Performance on the balance platform mediated 17% of
230 the association between age and visuospatial memory such that older participants who showed
231 increased sway also presented with poorer performance on the visuospatial memory factor (see
232 Figure 3 in the supplementary text).

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

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

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

244 Two combinations of mediators were applied. The first examined the influence of
245 psychiatric variables on visuospatial memory including the BDI, BAI and VSS_SA (Vertigo
246 Symptom Scale-Somatic Anxiety). The VSS_SA was treated as a mediator in this model
247 because the symptomology assessed by this scale is strongly associated with anxiety, and
248 reflect patients' psychiatric and somatic responses to the balance problem (Yardley et al.,
249 1992). A second model estimated whether the presence of fatigue and sleep disturbance exerted
250 an indirect influence on visuospatial memory using the FSS, ESS and PQI. As these comorbid
251 measures all involved self-reported perceptions of wellbeing for which no prior predictions
252 were held about their independence, covariance paths were drawn between the three test
253 residuals in each model.

254 Nested models were fit and compared for each combination of mediators (see Figures
255 2A and 2B). The first model tested the strength of the indirect paths involving the mediators
256 (psychiatric or sleep/fatigue) to establish whether a significant association was present. A
257 second model then added the direct path to evaluate the strength of the indirect relationship
258 once the direct path between the balance platform and visuospatial memory had been controlled
259 for. Four models were fitted and tested, all adjusted for age.

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

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

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

282

283 **Discussion**

284 Patients with vestibular dysfunction are often depressed, anxious, tired and have difficulty
285 concentrating and remembering (Bigelow et al., 2015; Grimm, Hemenway, Lebray & Black,
286 1989; Lahman et al., 2014). We have shown in the cohort of patients studied here, most of
287 whom have been diagnosed with vestibular migraine, that these co-morbidities frequently
288 occur together. There are few existing prevalence estimates of memory impairment,

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

297 The close relationship uncovered by the mediation analysis between vestibular and
298 short-term memory processes is perhaps surprising because it is reliant on indirect anatomical
299 connections. These connections are believed to take four main routes from the vestibular
300 nucleus complex to the hippocampus, three of which are thalamo-cortical and pass through the
301 cerebellum, parietal cortex and para-/post-subiculum respectively. The fourth route projects to
302 the hippocampal complex via the supramamillary nucleus and medial septum (Hitier et al.,
303 2014). According to Balaban and colleagues (2011), these ascending pathways support a
304 number of cognitive and interoceptive functions, sharing serotonergic and nor-adrenergic
305 inputs from vestibular-dorsal raphe nucleus and vestibular-coeruleus pathways. These
306 ascending pathways provide a substrate through which vestibular disorder can cause memory
307 impairment. Although the correlational basis of mediation analysis prevents attribution about
308 whether, in our study participants, the vestibular deficit caused the memory problem, support
309 for such an idea can be taken from the fact that participants only began to report memory
310 impairment after their vestibular symptoms took hold. In line with this self-report, participants'
311 referral notes did not highlight pre-existing memory problems, and our study exclusion criteria
312 out-ruled individuals with a prior neurological or psychiatric history that, inter alia, included
313 amnesic episodes. Coupled with the fact that we cannot find report of individuals with amnesia

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

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

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

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

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

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

372
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591 Table 1. Participant demographics

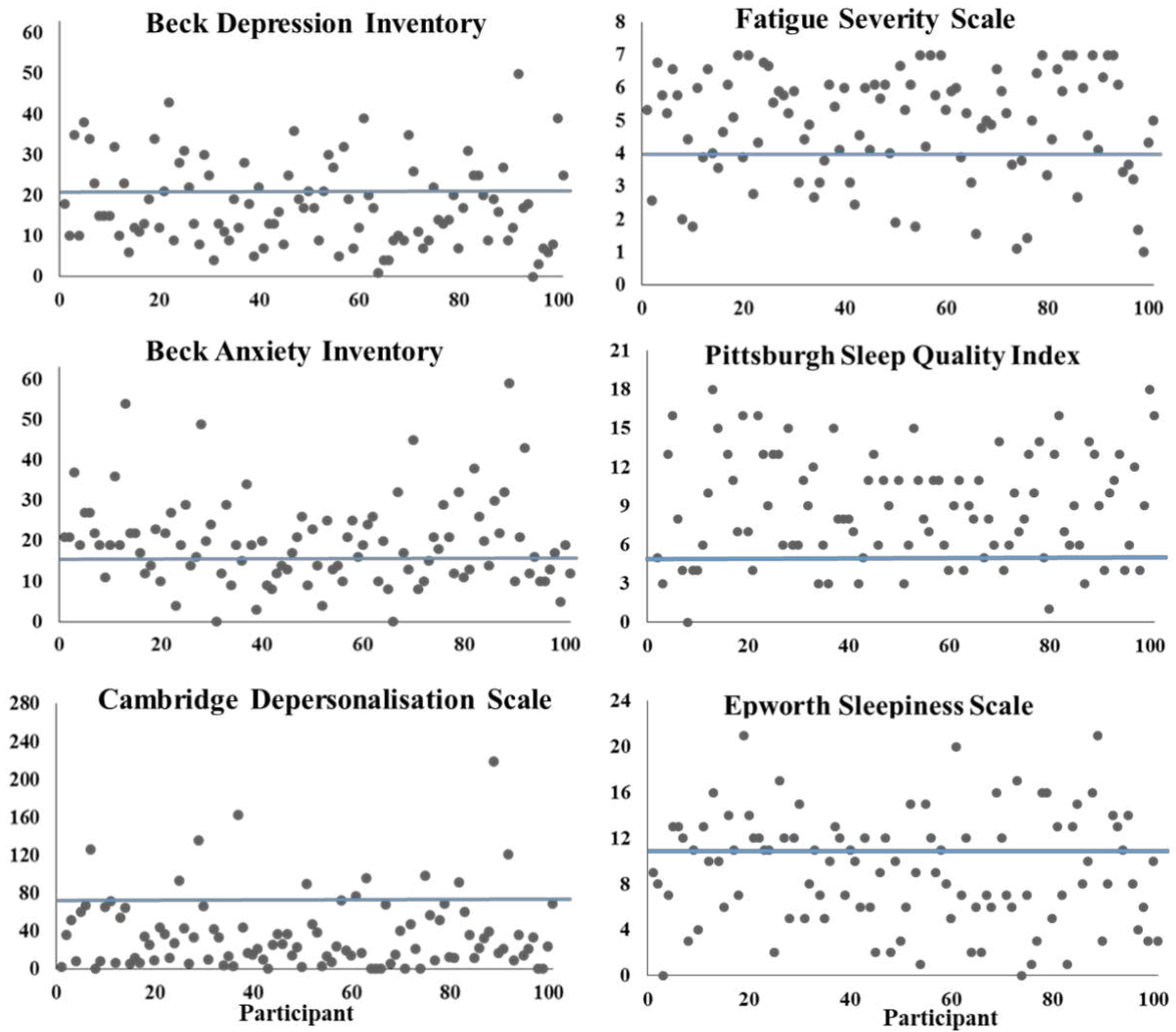
Diagnosis	N	%	Age		Gender		Constantly Presenting	
			M	SD	Male	Female	Yes	No
VM*	64	63.4	43.9	14.1	13	51	47	17
BPPV	8	7.9	59.5	11.4	1	7	5	3
BVF/ hypofunction	3	3	58.7	5.1	1	2	3	0
VM & BPPV	7	6.9	53.6	8.5	0	7	4	3
VM & peripheral loss	6	5.9	46.5	15.1	3	3	6	0
MD	2	2	54.5	12.2	1	1	1	1
Central dysfunction	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

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

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604 Figure 1. Relative incidence (%) of psychiatric and fatigue/sleep morbidities across the 101

605 participants. Horizontal lines show established clinical cut-offs.

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612 Table 2. Descriptive statistics and relative incidence (%) of cognitive morbidity, as measured

613 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

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

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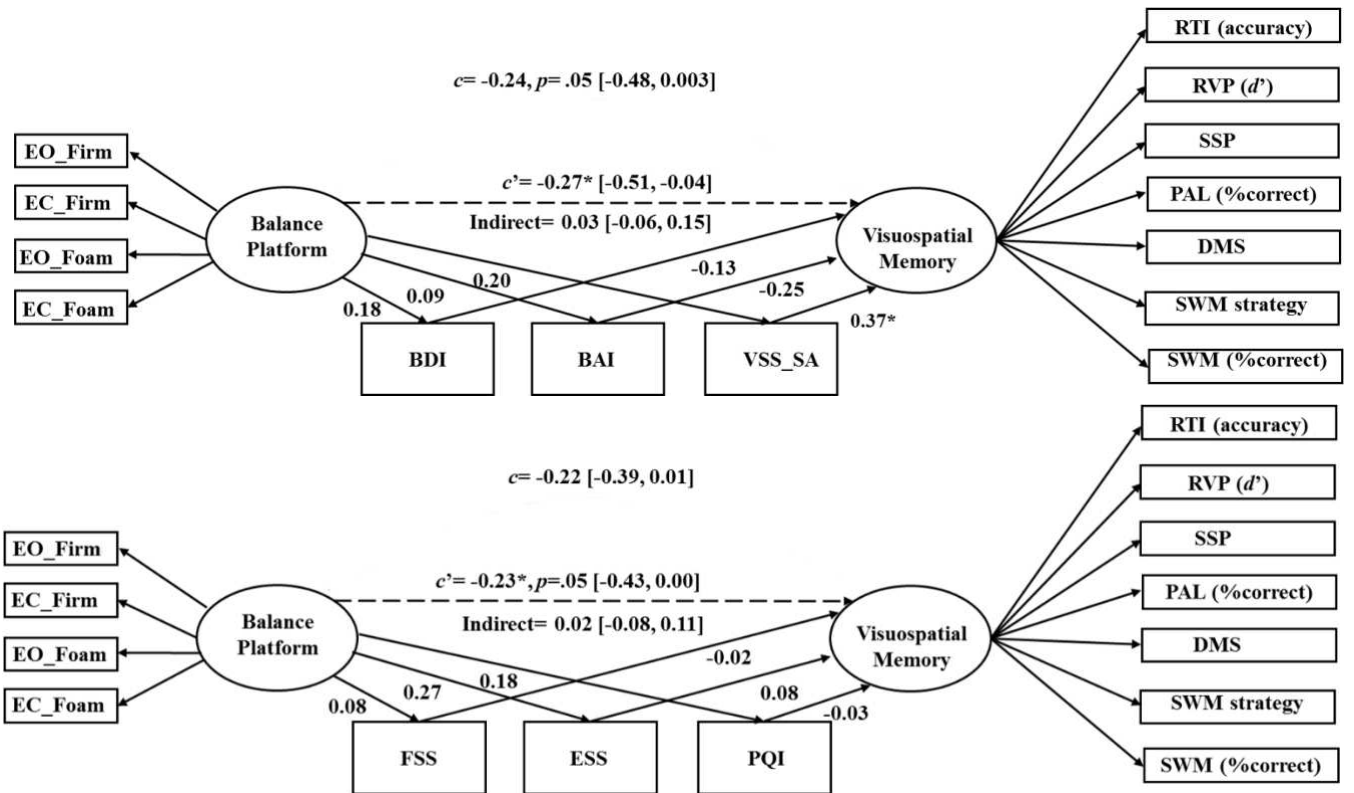
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626 Figure 2. Mediation models for the psychiatric (A) and fatigue (B) variables with direct paths
 627 (dashed lines).

628 * Standardised coefficients are reported alongside bias-corrected 95% confidence intervals

629 and significance values, * $p < .05$, ** $p < .01$. All 95% CIs were derived from bootstrapping

630 estimations after 2,000 simulations. Errors from the SWM strategy and SWM (%correct)

631 indicators were allowed to correlate to account for method effects, as well as errors from the

632 self-report questionnaires. Latent factors utilised the scale of the most conceptually relevant

633 observed variable in accordance with the factor loadings. All results were adjusted for age.

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638 Table 3. Chi-square difference (χ^2) tests between mediation models which freely estimated or
 639 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.
Psychiatric Indirect & Direct	$\chi^2(78, N = 95) = 120.08,$ p= .002 CFI= .93 RMSEA= .08	The addition of the direct path significantly improved model fit (>3.841 critical χ^2 difference for 1 df).
Fatigue Indirect	$\chi^2(79, N = 95) = 140.35,$ p<.001 CFI= .89 RMSEA= .09	140.35 – 136.90 = 3.45.
Fatigue Indirect & Direct	$\chi^2(78, N = 95) = 136.90,$ p<.001 CFI= .90 RMSEA= .09	The addition of the direct path did not significantly improve model fit (<3.841 critical χ^2 difference for 1 df).

640 Note. Chi-square difference (χ^2) tests were calculated using the formula: $\chi^2 \text{ diff} = \chi^2 \text{S} - \chi^2 \text{L}$
 641 and $\text{df diff} = \text{dfS} - \text{dfL}$, where “S” denotes the smaller model with fewer parameters to
 642 estimate and therefore more degrees of freedom, whereas “L” denotes the larger model with
 643 more parameters and therefore fewer degrees of freedom. This χ^2 diff-value is distributed
 644 with df diff degrees of freedom and can be checked manually for significance using a χ^2 table
 645 (Werner & Schermelleh-Engel, 2010).

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