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Factors influencing clinical outcome in vestibular neuritis – A focussed review and reanalysis of prospective data

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ABSTRACT

Following vestibular neuritis (VN), long term prognosis is not dependent on the magnitude of the residual peripheral function as measured with either caloric or the video head-impulse test. Rather, recovery is determined by a combination of visuo-vestibular (visual dependence), psychological (anxiety) and vestibular perceptual factors. Our recent research in healthy individuals has also revealed a strong association between the degree of lateralisation of vestibulo-cortical processing and gating of vestibular signals, anxiety and visual dependence. In the context of several functional brain changes occurring in the interaction between visual, vestibular and emotional cortices, which underpin the aforementioned psycho-physiological features in patients with VN, we re-examined our previously published findings focusing on additional factors impacting long term clinical outcome and function. These included: (i) the role of concomitant neuro-otological dysfunction (i.e. migraine and benign paroxysmal positional vertigo (BPPV)) and (ii) the degree to which brain lateralisation of vestibulo-cortical processing influences gating of vestibular function in the acute stage. We found that migraine and BPPV interfere with symptomatic recovery following VN. That is, dizziness handicap at short-term recovery stage was significantly predicted by migraine ($r = 0.523$, $n = 28$, $p = .002$), BPPV ($r = 0.658$, $n = 31$, $p < .001$) and acute visual dependency ($r = 0.504$, n = 28, $p = .003$). Moreover, dizziness handicap in the long-term recovery stage continued to be predicted by migraine ($r = 0.640$, $n = 22$, $p = .001$), BPPV ($r = 0.626$, $n = 24$, p = .001) and acute visual dependency ($r = 0.667$, n = 22, $p < .001$). Furthermore, surrogate measures of vestibulo-cortical lateralisation were predictive of the amount of cortical suppression exerted over vestibular thresholds. That is, in right-sided VN patients, we observed a positive correlation between visual dependence and acute ipsilesional oculomotor thresholds (R^2 0.497; $p < .001$), but not contralateral thresholds (R^2 0.017: $p > .05$). In left-sided VN patients, we observed a negative correlation between visual dependence and ipsilesional oculomotor thresholds (R^2 0.459; $p < .001$), but not for contralateral thresholds (R^2 0.013; $p > .05$). To surmise, our findings illustrate that in VN, neuro-otological co-morbidities retard recovery, and that measures of the peripheral vestibular system are an aggregate of residual function and cortically mediated gating of vestibular input.

1. Introduction

Vestibular neuritis (VN) is the most common cause of acute, continuous, non-positional vertigo. It is assumed to be of either viral origin [1], attributable to possible reactivation of latent herpes virus simplex type 1 [2] or alternatively due to a vascular ischemic event [3]. Contrary to what textbooks describe, many VN patients report long term dizziness and imbalance, however, which factors precisely determine a good or poor clinical outcome is a topic of active research.

Other common causes of dizziness and vertigo, such as benign paroxysmal positional vertigo (BPPV) and migraine, are good candidates to contribute deleteriously to long term symptomatic outcome in VN, and this certainly agrees with clinicians' experience. BPPV frequently develops in the aftermath of an acute VN episode due to degradation of otoconia which then lodges into the posterior semi-circular canal [4,5]. Furthermore, vestibular vertigo is a recognised trigger for migraine

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attacks and indeed the relationship between migraine and vertigo can be described as bi-directional, each possessing the ability to trigger the other one off [6].

Critically, we believe that to-date there is no prospective data available assessing the role for BPPV and migraine in long term dizzy symptoms in patients following VN. As these data had been collected, but not reported in a previous study that assessed psychological and psycho-physical data in VN [7], the first objective of this study is to present them here.

Beyond the vestibular nerve, central connections subdivide the vestibular system into four sub-systems: the vestibulo-ocular, the vestibulo-spinal, the vestibulo-autonomic and the vestibulo-cortical or vestibulo-perceptual systems. The vestibulo-ocular reflex (VOR) has been studied extensively due to the relative ease with which eye movements can be recorded [8]. Both basic and clinical physiological principles have been established with VOR studies, but it is unknown whether similar properties are present in fellow vestibular subsystems, particularly the vestibulo-perceptual (cortical) system. A practical reason to investigate vestibulo-perceptual function in VN is that, as mentioned, significant numbers of patients do not fully recover from an episode of VN, as well as the fact, that dizziness is in essence a subjective, perceptual symptom [9].

1.1. Vestibular perception as predictor of recovery after vestibular neuritis

Usually VOR and vestibulo-perceptual time constants are well matched, but they can dissociate in adaptive states in healthy individuals [10] and disease [11]. Indeed, this is what happens in the acute phase of VN [9] where vestibulo-perceptual time constants are shorter and more symmetrical than VOR time constants. This suggests somewhat better compensation at cortical (perceptual) than at brainstem (vestibulo-ocular) level. Although this central mechanism might provide a "shut down", "anti-vertiginous" effect in the acute phase, it does not predict long term symptomatic recovery in VN patients [7]. Further, regarding thresholds, both vestibulo-ocular and vestibulo-perceptual thresholds have been shown to be asymmetrically elevated (greater for ipsilesional rotations) following acute VN but again they reveal no long-term predictive fidelity for post VN symptoms [9].

Other high-order vestibular processing mechanisms, however, do relate to clinical recovery in VN patients. During asymmetric rotation [12] persistent vestibulo-perceptual dysfunction in VN patients was observed and it was noted that compensation of self-motion perception after VN was slower and less complete than that of the VOR [13]. Of clinical significance, perceptual but not vestibulo-ocular reflex deficits correlated with dizziness-related handicap, supporting the view that dysfunction of high-order central compensatory mechanisms plays a part in perpetuating vestibular symptoms [13].

1.2. Visual dependence, psychological features and hemisphere lateralization

Our previous work also identified that increased visual dependence and arousal/emotional factors were associated with poor long-term prognosis in VN patients [7]. Given the strong neural interaction between vestibular and visual inputs it is not surprising that visual dependence (= how much a person relies on vision for spatial orientation) is an important predictor of clinical outcome. What was particularly interesting, and unexpected, was that high levels of visual dependence were inextricably associated to psychological factors, such as anxiety and depression [7].

Visual dependence can easily be measured by the magnitude of visually elicited postural responses [14] or by the amount of subjective tilt induced by a rotating visual background to a vertical line viewed by the subject (e.g. in a visually dependent subject the rotating background induces a larger tilt of the subjective visual vertical). One way how visual dependence may influence outcome in VN patients is via cortically mediated gating of vestibular input that feeds into higher levels of the CNS [15].

Our recent work in healthy individuals has demonstrated that greater right-hemisphere dominance for vestibulo-cortical processing is associated with, a) reduced visual dependence [16], b) gating of vestibulo-ocular thresholds [17], c) increased postural stability [18] and, d) lower trait anxiety scores [19]. Thus, increased right hemispheric dominance for spatial processing seemingly downregulates the risk factors of poor long-term outcome following VN, namely anxiety, visual dependency, and motion sensitivity [20]. This notion is in line with findings from neuroimaging studies that probe central compensation mechanisms which occur following unilateral vestibular loss. These studies have, a) implicated signal changes within the multisensory vestibulo-cortical areas, visual cortical and affective areas [21–24], b) illustrated reduced interhemispheric vestibulo-cortical functional connectivity (see for review) [25], and c) revealed hemispheric-dependence as demonstrated by differences in cortical responsiveness when comparing right versus left-sided vestibular neuritis patients [26].

Accordingly, the bringing together of our experimental work in healthy individuals [20] with imaging data [21–24] from the literature, it presents the case for a re-analysis of our previously collected behavioural data in VN patients [7], to elucidate if differences in surrogate measures of brain lateralization can predict the degree of gating upon vestibular input as the secondary objective of this present study.

Research questions:

Here we retrospectively reanalyse our previous data [7] to address two specific research questions potentially involved in long term symptomatic prognosis in VN.

1) Does the presence of concomitant vestibular (BPPV) and neurological disease (migraine) impact clinical outcome.

2) Can surrogate markers of vestibulo-cortical lateralization predict the degree of cortical gating upon residual peripheral function.

2. Material and methods

2.1. Subjects

For question 1) we reanalysed 40 patients (mean age 50 years, range 22–79, 18 females) but for question 2) we could only use 34/40 patients (mean age 44.6 years, range 22–72, 15 females: 21 with right-sided VN; 13 with left-sided VN), as 2 patients were left-handed (confounder for brain laterality research) and in 4 patients there was no data regarding handedness. All patients used were studied prospectively in the acute phase of VN (1–5 days after onset, median = 2 days), recruited with acute vertigo in our emergency department. As previously reported [7] clinical examination revealed a unidirectional horizontal nystagmus, a positive horizontal head impulse test, unilateral canal paresis on caloric testing (>20%), unsteadiness and no hearing or CNS involvement. For question 1, thirty-two patients were studied in the recovery phase (median = 10 weeks). Twenty-six of these patients were also seen in a long-term recovery stage (median = 10 months).

Symptomatic recovery was assessed using the Dizziness Handicap Inventory (DHI) which measured the perceived handicapping effects of dizziness. As described in our previous work [7], a normalised score (0–4) was calculated by dividing total score by number of questions answered and used as an overall measure of recovery (0–1.3 = nil to mild handicap, 1.4–2.6 = moderate handicap and 2.7–4 = severe handicap). Informed consent (at the time of the original study, when data were collected) was obtained from all patients as approved by Charing Cross Hospital Ethics Committee.

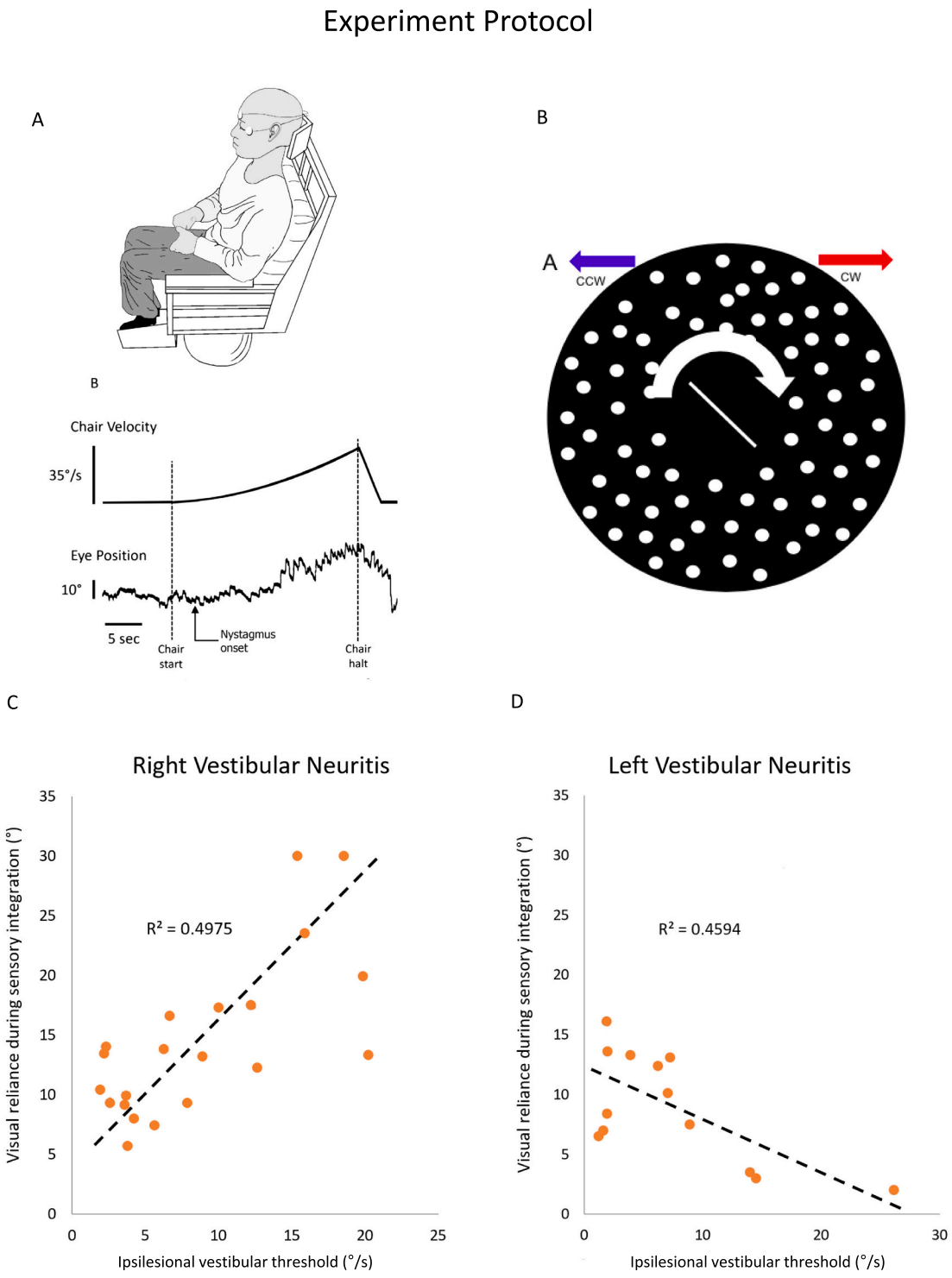

Fig. 1. A) Illustration of the methodology to collect the VOR thresholds. Participants were securely seated in a motorized rotating chair which could rotate to either the right or left. An example of the acceleration profile of a rightward rotation is shown, directly above the associated eye movement response which was recorded using EOG. B) The rod and disk task. Participants had to set the rod to the perceived gravitational vertical during no background-dot motion, clockwise and anti-clockwise background motion (randomized order). C & D) Here on the x-axis we represent the ipsilesional oculomotor thresholds in deg./s and on the y axis the measure of visual dependence in degrees (tilt of the vertical rod induced by the rotating visual background). As shown we observed a positive correlation between these two measures in patients with right-sided VN (3C) and a negative correlation in patients with left-sided VN (3D).

3. Methodology for Q1) Does the presence of concomitant vestibular (BPPV) and neurological disease (migraine) impact clinical outcome

3.1. Migraine

Presence of migraine was assessed using the Migraine Screen Questionnaire (MS-Q) [27], administered at the time of the visits for the original study [7]. The validated tool assesses the following items: frequency, intensity duration of headache, nausea, sensitivity to light/noise and disability. Each item is scored on a yes/no scale, with each yes answer equivalent to one point. A score of four or more points denotes presence of migraine.

3.2. Benign paroxysmal position vertigo

Patients were assessed clinically during follow up by an experienced neuro-otologist and diagnosis of BPPV was made via a positive Dix-Hallpike test. If positive, patients were treated using the Epley or Semont manoeuvres.

4. Methodology for Q2) Can surrogate markers of vestibulo-cortical lateralization predict the degree of cortical gating upon residual peripheral function

Based on the premise that brainstem mediated vestibulo-ocular thresholds are cortically gated [17], we postulated that the variance in ipsilesional vestibular thresholds in the acute stage may be correlated with surrogate markers of hemispheric dominance. In order to test this, we used visual dependency measures as an indirect surrogate measure of cortical lateralisation and correlated this with the VOR thresholds separately for right and left-sided VN patients. (N.B.: Our previous work using neuromodulation in healthy individuals has shown that individuals with greater right hemisphere dominance for vestibular processing are less visually dependent) [16].

4.1. Motion thresholds

We previously reported in Cousins et al., how we assessed motion detection (vestibular ocular and perceptual thresholds) in acute VN. In this present analysis, we are only interested in vestibular-ocular thresholds as the specific question we are probing is how cortical processes gate low-level vestibular input. As illustrated in Fig. 1A, as per original study [7], we measured this by having patients seated securely on a vibration-free motorized rotating-chair (Contraves, USA) in darkness and with white noise delivered through headphones. Six rotations were performed (3 right and 3 leftwards; randomized order) with each rotation starting from rest with an initial acceleration of $0.3^{\circ}/s^2$, increasing by $0.3^{\circ}/s^2$ every 3 s, as previously reported. The incremental acceleration continued until a consistent vestibular nystagmus was observed to provide the vestibular-ocular thresholds [7].

4.2. Visual dependency

As previously reported, in Cousins et al. [7], visual dependence was measured with the rod-and-disk task on a laptop computer (program available at: http://www.imperial.ac.uk/medicine/dizzinessandvertigo). Patients sat in front of the screen with the head held against an attached viewing cone to block extraneous visual cues (eye-screen distance 30 cm). As illustrated in Fig. 1B, the stimulus consisted of a luminous white 6 cm rod against a black background filled with randomly distributed white dots. Patients had to align the rod to their perceived vertical (subjective visual vertical) with a roller mouse, from initial random rod settings 40° away from vertical, during four trials in three conditions: background dots stationary and dots rotating clockwise and counter-clockwise. Visually induced rod tilt illusion was calculated as a measure of visual dependence for each subject. First, static tilt was calculated as the mean rod tilt in the four trials with background dots stationary. Then, visually induced rod tilt was calculated as the mean of the absolute values of the rod tilt from each trial with dots rotating minus the static rod tilt [7].

5. Results

Q1) Does the presence of concomitant vestibular (BPPV) and neurological disease (migraine) impact clinical outcome

Symptom load (DHI score) decreased from acute (mean 2.13: SD 1.02) to short-term (mean 0.63 SD 0.95) and long-term (mean 0.38 SD 0.81) recovery stages. Three patients were diagnosed with BPPV (9.7%) and seven with migraine (25%) during the recovery stages. Step-wise linear regression was used to assess the predictive relationship between migraine, BPPV and acute visual dependency on symptomatic recovery (DHI) at short (10 weeks) and long-term (10-months) recovery stages.

5.1. Short-term symptomatic recovery (10 weeks)

DHI at short-term recovery stage was significantly predicted by migraine ($r = 0.523$, $n = 28$, $p = .002$), BPPV ($r = 0.658$, $n = 31$, $p < .001$) and acute visual dependency ($r = 0.504$, n = 28, $p = .003$). The best model that emerged from the regression analysis with DHI at short-term recovery stage as dependent variable, and migraine, BPPV and visual dependency entered as predictor variables included migraine and BPPV [$F(2,21) = 12.175$, $p < .001$, $R^{2=}0.537$, $R^2_{Adjusted} = 0.493$]. To note, acute visual dependency dropped out suggesting a high degree of collinearity with migraine and BPPV.

5.2. Long-term symptomatic recovery (10 months)

DHI at long-term recovery stage continued to be predicted by migraine ($r = 0.640$, $n = 22$, $p = .001$), BPPV ($r = 0.626$, $n = 24$, $p = .001$) and acute visual dependency ($r = 0.667$, n = 22, $p < .001$). The most significant emergent model included acute visual dependency and migraine [$F(2, 19) = 17.029$, $p < .001$, $R^2 = 0.642$, $R^2_{Adjusted} = 0.604$] as predictors of symptoms at the long-term stage.

Q2) Can surrogate markers of vestibulo-cortical lateralization predict the degree of cortical gating upon residual peripheral function.

In right-sided VN patients, we observed a positive correlation between visual dependence and acute ipsilesional oculomotor thresholds (R^2 0.497; $p < .001$; Fig. 1C), but not contralateral thresholds (R^2 0.017: $p > .05$). In left-sided VN patients, we observed a negative correlation between visual dependence and ipsilesional oculomotor thresholds (R^2 0.459; $p < .001$; Fig. 1D), but not for contralateral thresholds (R^2 0.013; $p > .05$). There was no relationship between the ipsilesional thresholds and function on the healthy side as assed via the contralateral thresholds (R^2 0.02; $p > .05$ right VN or R^2 0.017; $p > .05$ left VN).

6. Discussion

6.1. Overview

Here we show how in addition to the previously identified factors that predict long term outcome in VN (i.e. visual dependency, anxiety, and their interdependence), factors such as the presence of other neurological (migraine) or otological disorder (BPPV) also hold predictive value. Furthermore, we show how the extent of brain lateralisation in vestibulo-cortical processing (indirectly measured as visual dependence) influences vestibular thresholds. This latter finding may partly account for why measures of residual peripheral vestibular function are a poor measure of functional outcome in VN, given that they may reflect an aggregate of residual function and central

compensation. Despite the associated limitation of our relatively small sample size, when taken together, these data directly speak to recent findings that indicate central compensation mechanisms account for about 40% of total contribution to recovery [28].

1) **Does the presence of concomitant vestibular (BPPV) and neurological disease (migraine) impact clinical outcome.**

Clinicians have long suspected that the concomitant presence of BPPV and migraine can influence clinical outcome in VN. Moreover, clinicians are becoming increasingly aware that laboratory assessment of peripheral vestibular function is a poor correlate of functional status [7]. These data provide quantitative support to this view and emphasise the need for clinicians to actively look for possible co-morbidities in particular migraine and BPPV. VN and head trauma are the two more common predisposing factors for so called secondary BPPV, with the former accounting for approximately 15% of all cases of BPPV [29].

Regarding migraine, the data reanalysed here suggests a close interaction between migraine and visual dependence. This association, and more specific examples such as sensitivity of optokinetic stimuli in migraine and vestibular migraine [30,31], has long been established [32–34]. The new finding is how this reciprocal association between migraine and visual dependence impact upon the outcome of VN patients. Although the numbers of patients we present here are relatively small to discuss these effects mechanistically, our statistical analysis suggest a high degree of collinearity between migraine and visual dependence with the latter variable dropping out in the individual statistical models. Although further work is needed to corroborate these findings, the current analysis suggest that it is migraine which drives the negative effect of visual dependence upon outcome in VN.

These data give a broader view to the treatment of the patient with long term consequences of VN. Patients need to be assessed pro-actively for the presence of migraine and BPPV as both conditions can be effectively treated. Visual dependence, its associated symptoms of visual vertigo (visually induced dizziness) are amenable to treatment with visuo-vestibular therapies [35] as well as the psychological components [36]. Early identification and treatment of these features might stop the development of chronic dizziness, often labelled as PPPD (Persistent Perceptual Postural Dizziness), a functional dizziness syndrome [37] in which both migraine and visual vertigo feature prominently.

2) **Can surrogate markers of vestibulo-cortical lateralization predict the degree of cortical gating upon residual peripheral function.**

Based on the premise that brainstem mediated vestibulo-ocular thresholds are cortically gated [17], we postulated that the variance in ipsilesional vestibular thresholds in the acute stage may be correlated with surrogate markers of hemispheric dominance. This is a timely question to address, as the structure and function of the vestibular cortex has now been relatively well described [38–41], and work has begun to illustrate its functional role upon vestibular behaviour not only in healthy individuals- see for review [42], but also in patients with VN [43], as well predicting clinical outcome following VN [22].

To probe sensory integration, we can measure an individual's ability to align a target to the perceived gravitational vertical (“earth upright”), both in the presence and absence of background visual motion (“rod and disk task”) [44]. In such a task, if verticality perception is strongly modulated by the introduction of background visual motion, then that individual preferentially favours visual over vestibular/proprioceptive cues during sensory integration and is said to be visually dependent. Previous human psychophysical data suggest that humans weigh sensory cues in proportion to the reliability of each signal (i.e. realistic probability), based on previous experiences (i.e. prior beliefs; Bayesian computation) [45–52], explaining why VN patients who have a less reliable signal exhibit larger visual errors that are associated with poor clinical outcome [53]. Our recent research has demonstrated that disruption of interhemispheric interactions between the posterior parietal cortices (PPC), a key node in vestibulo-cortical processing, can predict weighting during sensory integration and modulate vestibular thresholds [17,54].

Accordingly, we postulated that visual dependence may similarly be subject to interhemispheric interactions associated with the emergent dominance in vestibulo-cortical processing in the PPC [42]. In line with this prediction, we observed a relationship between visual dependence and the degree of vestibulo-cortical dominance - as measured by the degree of suppression of caloric vestibular nystagmus, following electrical (tDCS) inhibition of the of left PPC [55,56]. Of note, previous research has illustrated strong cortical influences upon vestibular nystagmus and vestibulo-ocular thresholds following non-invasive electrical stimulation to modulate cortical excitability over the parietal cortex [17,55,56] as well as parietal lesion data in patients [57]. With regards to the visual dependency data, we observed that less right hemisphere dominant individuals, as reflected by a lower nystagmus suppression index following application of cathodal tDCS over the left hemisphere, had increased visual dependency measures. Thus, greater right hemispheric vestibulo-cortical dominance is associated with increased reliance on gravito-inertial cues during performance of the rod and disk task [16].

Based on the above findings, it appears that the degree of visual dependence reflects vestibulo-cortical dominance and thus can be implemented as a surrogate marker of dominance. In order to test our specific question of whether the degree of vestibulo-cortical lateralization predicts the extent of cortical gating upon lower-level vestibular function, we used visual dependency measures as an indirect surrogate measure of cortical lateralisation and correlated this with the VOR thresholds separately for right and left-sided VN patients.

As shown in Fig. 1C, in patients with right-sided VN we observed a significant positive correlation between visual dependence (surrogate of cortical dominance) and ipsilateral (i.e. rightward rotations) but not contralateral (i.e. leftward rotations) oculomotor thresholds. In patients with left-sided VN we observed a significant negative correlation between visual reliance and ipsilateral (i.e. leftward rotations: Fig. 1D) but not contralateral (i.e. rightward rotations) oculomotor thresholds.

VN results in a tonic imbalance and as a result in the acute stage patients have a resting nystagmus. Following a right VN, there is a left-beating resting nystagmus due to the tonic imbalance which preferentially activates the left hemisphere [38]. Accordingly, during rightward rotations that elicit a right beating nystagmus the right hemisphere is required to inhibit the left hemisphere in order to process the right-beating vestibular nystagmus (i.e. rightward rotation elicits a right beating nystagmus preferentially processed by the right hemisphere). Accordingly, those right-sided VN patients with lower visual reliance measures during the sensory integration task (i.e. more right hemisphere dominant) can more easily inhibit the left hemisphere and accordingly generate the right beating vestibular nystagmus more quickly in response to rightward rotations in comparison to those patients that exhibit less right hemispheric dominance (i.e. more visually reliant) [16].

Conversely, following left-sided VN, the tonic imbalance causes a right-beating resting nystagmus which preferentially activates the right hemisphere, whereas leftward rotations induce left-beating vestibular nystagmus mediated by the left hemisphere [38]. Thus, in this scenario the left hemisphere is required to inhibit the right in order to generate the left-beating vestibular nystagmus (leftward rotation). Accordingly, those individuals who are less visually reliant (i.e. right hemisphere dominant) are less readily able to inhibit the right hemisphere and hence generate left beating vestibular nystagmus more slowly in response to leftward rotations [16].

No relationship was observed between contralateral oculomotor thresholds and hemispheric dominance in either right or left-sided VN; as in these conditions, as there is no interhemispheric conflict as both the

resting nystagmus and rotational nystagmus implicate the same hemisphere. Furthermore, we observed no relationship between the variance in ipsilateral thresholds and function of the healthy labyrinth as assessed by contralateral thresholds.

Our findings support a tentative link between the degree of hemispheric dominance and amount of cortical modulation exerted over the brainstem-mediated vestibulo-ocular reflex. These findings also fit an interhemispheric account of how higher order mechanisms gate subcortical vestibular function [42].

7. Concluding remarks

Here we show that migraine and BPPV interfere with symptomatic recovery following VN. Migraine and dizziness bi-directionally influence one another and our findings here support this. In addition, visual dependence, a general predictor of outcome in VN and a surrogate measure of the degree to which vestibulo-cortical processing is lateralised, were predictive of the amount of cortical suppression exerted over low-level vestibular function. This suggests that measures of peripheral vestibular function are an aggregate of residual function and cortically mediated gating of vestibular input, thus perhaps the reason why they are not predictive of prognosis.

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