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Predictors of clinical recovery from vestibular neuritis: a prospective study

Sian Cousins[1] PhD, Diego Kaski[1] MRCP PhD, Nick Cutfield[2] MD FRACP, Qadeer Arshad[1] PhD, Hena Ahmad[1] MRCP, Michael A. Gresty[1] PhD, Barry M. Seemungal[1] PhD FRCP, John Golding[3] PhD, Adolfo M. Bronstein[1] MD PhD FRCP

[1]Neuro-otology Unit, Division of Brain Sciences, Imperial College London, Charing Cross Hospital, London, United Kingdom
[2]Neurology, Dunedin Hospital, University of Otago, Dunedin, New Zealand
[3]Department of Psychology, University of Westminster, London, United Kingdom

Corresponding author:
Prof Adolfo Bronstein
Neuro-otology Unit,
Imperial College London,
Charing Cross Hospital,
London W6 8RP.
Email: a.bronstein@imperial.ac.uk
Phone: +44 20 3311 7523 Fax: + 44 20 3311 7577

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Abstract

We sought to identify predictors of symptomatic recovery in Vestibular Neuritis (VN). Forty VN patients were prospectively studied in the acute phase (median=2 days) and 32 in the recovery phase (median=10 weeks) with vestibulo-ocular reflex, vestibular-perceptual and visual dependence tests and psychological questionnaires. Clinical outcome was Dizziness Handicap Inventory score at recovery phase. Acute visual dependency and autonomic arousal predicted outcome. Worse recovery was associated with a combination of increased visual dependence, autonomic arousal, anxiety/depression and fear of bodily sensations, but not with vestibular variables. Findings highlight the importance of early identification of abnormal visual dependency and concurrent anxiety.

Introduction

Acute vertigo due to vestibular neuritis (VN), resolves over a matter of days but 30-50% of patients develop disabling chronic dizziness[1]. Identifying predictors of the "acute-to-chronic" dizziness transition would allow patients at high risk of chronic dizziness to be targeted with focused therapies. Two possible predictors have been identified; follow up studies[2, 3] have shown that psycho-pathological features facilitate long-term dizziness, however, cross-sectional studies indicate that psycho-physical estimates of how much an individual relies on vision for spatial orientation ("visual dependence") is also associated with chronic dizziness[4, 5]. As psychological questionnaires and psycho-physical estimates of visuo-vestibular interaction assess different functional domains, we now report a prospective study of VN patients examining visual dependence (rod-and-disk test), psychological features, as well as vestibulo-reflex and vestibulo-perceptual function. The aim is to establish how these variables interact to predict clinical outcome in VN.

Method

Forty patients (mean age 50 years, range 22-79, 18 females) were studied prospectively in the acute phase of VN (1-5 days after onset, median=2 days) and 32 patients in the recovery phase (median=10 weeks). Twenty-six of these patients were also seen in a long-term recovery stage (median=10 months) to validate acute and recovery stage findings. Acute clinical examination revealed unidirectional horizontal nystagmus with a torsional component, a positive horizontal head impulse test[6], unilateral caloric canal paresis, lateropulsion and no hearing impairment or symptoms/signs of CNS disorder[7]. Of the 24 patients who were administered prochloperazine, only 3 received these on the day of testing, but the drug has been shown to have no effect upon vestibulo-reflex or vestibulo-perceptual function [8]. MRI brain scans were not routinely performed, but when done on hospital arrival (n=3), no abnormalities were detected. No patient received corticosteroids. Patients were strongly advised to remain physically active and were explained the benefits of doing so but, in the acute phase, none were referred for formal physiotherapy.

In light of the aim of this study to assess how psychological variables interact with vestibulo-reflex, vestibulo-perceptual measures and visual dependency, at each stage patients underwent bithermal caloric testing (30-44°C) and the following test battery:

The **Threshold vestibular task** (details in Cousins et al. 2013[9]) measures vestibular-perceptual (VP) thresholds for detection of angular motion. The test comprised 3 rightward and 3 leftward rotations, with an initial acceleration of 0.5deg/s^2, increasing by 0.5deg/s^2 every 3s. Patients sat on a rotating chair with a hand-held device with two buttons and were asked to press the button corresponding to their perceived direction of rotation (leftward/rightward) during each rotation. Vestibular-perceptual thresholds were measured by the time taken from chair acceleration onset to button press.

The **Supra-threshold vestibular task** (details in Cousins et al[9]) measures vestibulo-perceptual responses to eight +/-90deg/s velocity steps lasting 60s with acceleration phase of 1s. Perceptual responses were recorded by patients turning a chair-fixed tachometer wheel to indicate their perceived rotational velocity during the four rotational and four post-rotational periods (starting-stopping Barany test). The tachometer output follows an approximately exponential decay allowing measurement of the time constant of decay and the duration of the perceptual response[9]. In this study we only used the latter to reduce the number of variables statistically analysed.

Rotations were performed using a vibration-free motorised rotating chair (Contraves, USA; fitted with chin and head rests) in the dark with sound masking to eliminate non-vestibular cues.

Rod-and-Disk Task[10]: Visual dependence was measured with the Rod-and-Disk test on a laptop computer (Figure 1A, B[5]; 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. The stimulus consisted of a luminous white 6cm 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° from vertical, during 4 trials in three conditions: background dots stationary and dots rotating at 30deg/s clockwise and counter-clockwise. Visually induced rod tilt 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. Mean absolute static tilt was used as a measure of otolith function.

Questionnaire measures:

Dizziness Handicap Inventory, DHI[11], measured the perceived handicapping effects of dizziness. 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). A normalised score was used as patients in

the acute stage were not able to answer all questions, for example 'Does walking down the aisle of a supermarket increase your problem?' The **Hospital Anxiety and Depression Scale**, HADS [12] measured state anxiety and depression. For each scale, scores ranged from 0 to 21 (high level of anxiety/depression). **The Body Sensations Questionnaire**, (BSQ) [13] measured the intensity of fear relating to body sensations, with scores ranging from 0-5 (extremely fearful) and the **Vertigo Symptom Scale_arousal** (VSS_A)[14] measured autonomic arousal components (e.g. heart pounding, excessive sweating; score 0-64).

The primary measure of outcome was symptomatic recovery as assessed with the Dizziness Handicap Inventory (DHI). Variables influencing symptoms at recovery (10Week_DHI) and long-term recovery (10Month_DHI) stages were investigated using correlational (Pearsons 'r') analysis. We used stepwise multiple linear regression to predict outcome from baseline (acute) variables, whereas we used exploratory factor analysis[15] to look for associations between significant variables and to assess whether these patterns of associations could be due to a small number of underlying factors (sometimes called unobserved or latent variables). Larzelere and Mulaik adjusted Bonferroni correction[16] was used. Informed consent was obtained from all patients as approved by Charing Cross Hospital Ethics Committee.

Results

Symptoms improved drastically from acute to recovery stages in all patients, with considerable individual variability (Figure 1, C). Average symptom load (Normalised DHI, score 0-4) decreased from 2.13SD1.02 acutely to 0.63SD0.95 at recovery stage (10Week). Results for all measures are summarised in Supplementary Table 1.

Predicting clinical recovery from the acute stage (Table 1A): DHI score at recovery stage (10Week_DHI) was significantly correlated with *acute* autonomic arousal (r=0.53, p=.002), acute visual dependency (r=0.5, p=.006) and acute fear of bodily sensations (r=0.35, p=.049, not significant after Larzelere and Mulaik adjusted Bonferroni correction[16]). Stepwise multiple linear regression to predict DHI at recovery (10Week) stage, entering all the baseline acute variables is shown in Table 1 as predictors, produced a significant model (adjusted R^2=0.562, ANOVA F=13.8, df 2,18, p<.001) in which the two significant predictors were acute autonomic arousal (beta=.47 p=.02) and acute visual dependency (beta=.41 p=.038).

Associations between variables at the recovery stage: Table 1B shows all bivariate correlations between symptoms at the recovery stage (10Week) and psychophysical, visual dependency, and psychological variables also at 10 weeks. Clinical outcome (10Week_DHI) correlated with vestibulo-perceptual thresholds (r=0.52, p=0.003), visual dependency (r=0.56, p=0.001) and, less significantly, with canal paresis (r=0.38, p=0.045, not significant after Larzelere and Mulaik adjusted Bonferroni correction[16]), all measured at 10 weeks. In addition, the following questionnaire data correlated with 10Week_DHI: anxiety and depression (HADS, r=0.71, p=<0.001), autonomic arousal (VSS_A, r=0.71, p<0.001) and fear of bodily sensations (BSQ, r=0.58, p=0.001).

Factor Analysis (Table 2) was used to further explore the significant correlations outlined above and describe the underlying pattern of associations between variables. The first statistical component identified by Factor Analysis accounted for 59% of the variance and, critically, loaded 10Week_DHI, our outcome variable. This first component also loaded visual dependency, autonomic arousal, fear of body sensations (BSQ, acute and recovery stages) and anxiety-depression scores (HADS, recovery stage). A second component was identified, accounting for just 12.9% of variance and loaded canal paresis and vestibular perceptual thresholds but, notably, did not include clinical outcome.

Long-term prognosis: Additional correlational analysis was carried out to assess whether factors determining symptomatic recovery outlined above, continue to predict symptom load at long term recovery (10Month_DHI). Comparisons between recovery (10Week) and long-term recovery (10Month) stages showed no significant change in symptom load (DHI) (Figure 1, C), confirming that most recovery takes place by week 10. Bivariate correlational analysis showed acute autonomic arousal (VSS_A; r.78, p=<0.001), visual dependency (r=0.67, p=0.001) and fear of bodily sensations (r=0.46, p=0.02) continue to predict long-term outcome (10Month_DHI).

There was no significant difference in the baseline measures of autonomic arousal, visual dependency or fear of bodily sensations between participants who returned at 10 weeks or 10 months and those who did not, suggesting drop-outs did not systematically distort results.

Discussion

We investigated how vestibular-reflex (caloric), vestibulo-perceptual, visual dependence (rod-and-disk) and psychological measures intertwine to predict clinical outcome in VN patients. Correlation and regression analyses showed that the main predictors of clinical recovery were increased levels of autonomic arousal (VSS_A) and visual dependence in the *acute phase*. Parameters in the *recovery phase* associated with clinical outcome were, again, visual dependency, anxiety/depression (HADS), autonomic arousal and fear of bodily sensations. Vestibulo-perceptual thresholds and, marginally, canal paresis at 10 weeks were also correlated with recovery. Critically, however, factor analysis revealed that visual dependency and questionnaire data loaded as a single factor, including the clinical outcome variable (10Week_DHI) and explained 59% of the variance. In contrast, the peripheral vestibular variables (caloric and threshold data) only accounted for 12.9% of the variance but, notably, did not include clinical outcome (Table 2).

Visual motion sensitivity and dizziness brought on by complex or moving visual surroundings are common in cross-sectional studies of chronically symptomatic vestibular patients[4]. Our prospective study shows that if too much weighting is placed on vision acutely (visual dependence), or if sensory integration mechanisms are unable to down-regulate the visual contribution to the central compensation process, patients recover poorly. Whilst prior studies have shown that anxiety, depression, and fear of body sensations are significantly associated with symptom recovery[2, 3], the novel finding is that it is the *combination* of psychological factors and visual dependence that best predicts clinical outcome. In agreement with previous studies, the degree of peripheral vestibular recovery (caloric, head-impulse test or VEMPs) bears little influence on global clinical outcome [17, 18].

Do autonomic arousal and psychological factors develop in response to heightened visual dependency, or vice-versa, or are they coexisting independent parameters? The latter seems less likely given that compensation after a unilateral vestibular lesion relies upon multi-sensory (visuo-vestibular) re-weighting, and central mechanisms subserving such functions are affected by psychological states[19]. A mechanistic link between visuo-vestibular compensation and psychological factors is underpinned by the presence of neuroanatomical networks processing visual, vestibular and emotional inputs [20, 21]. Moreover, fMRI data during simulated vertigo suggest an association between psychological traits and functional connectivity patterns within visuo-vestibular and anxiety-related cortical networks[22], but the directionality of this association remains unclear. Our findings highlight a) the importance of early identification of abnormal visual dependency and concurrent anxiety in VN and b) the potential for early treatments to improve long-term outcome by reducing visual dependency (sensory re-weighting strategies;[23, 24]) and combining pharmacotherapy and cognitive therapies to reduce anxiety and autonomic arousal. Further work should characterise the mechanism by which visual dependency is up-regulated in such patients, in relation to increased anxiety, to allow more targeted therapies at the early phase of a vestibular injury.

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Author contributions

SC was responsible for recruitment of participants and conducting testing, data analysis, statistical analysis, interpretation of data, manuscript development and revisions. DK recruited participants, conducted testing and was involved with interpretation of data, manuscript development and revisions. NC recruited participants and conducted testing and was involved with interpretation of data and manuscript revisions. QA conducted participant testing and was involved with interpretation of data. HA recruited participants and conducted testing. MAG was involved in study concept and design, interpretation of data and study supervision. BMS recruited participants, and was involved in interpretation of data and critical revision of manuscript. JG conducted statistical analysis and was involved in revision of manuscript. AMB was responsible for study concept and design, interpretation of data and was involved in all revisions of manuscript.

Conflicts of Interest

The authors declare no conflicts of interest

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Figure 1

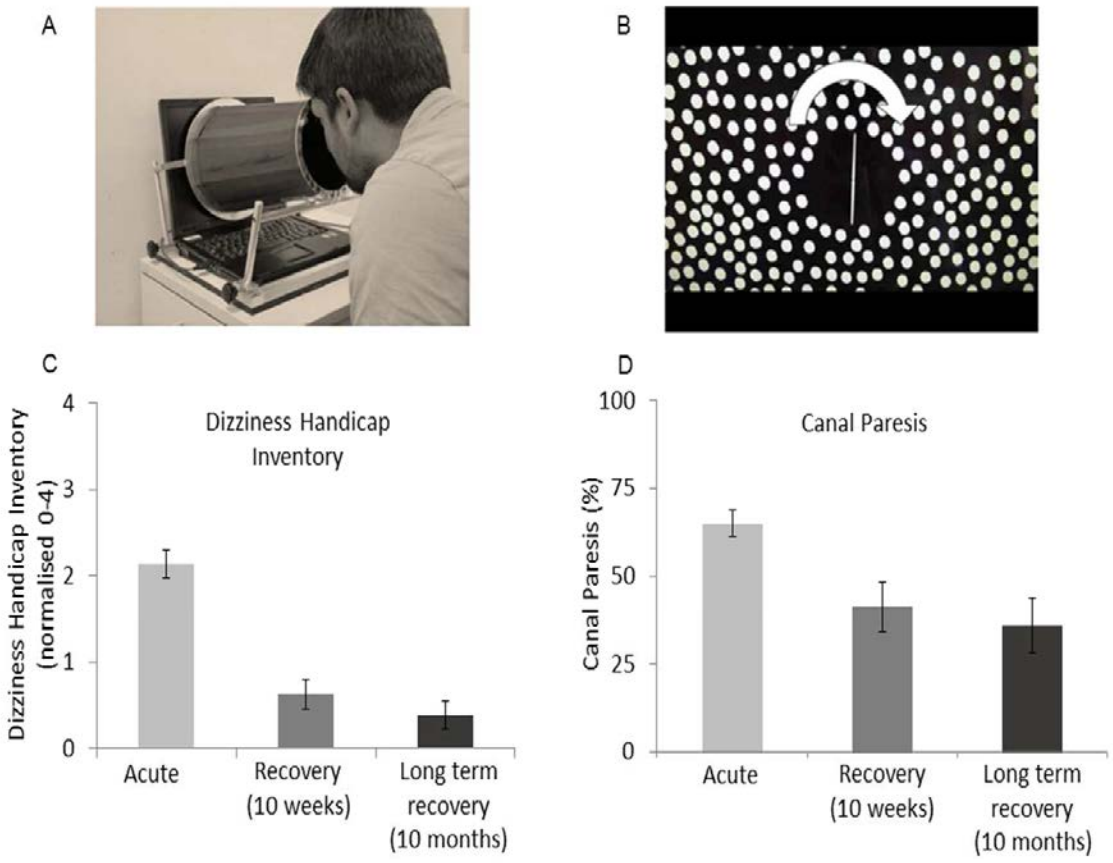

Figure 1

A. Laptop-based Rod-and-Disk test to measure visual dependency, showing a subject viewing the screen through a field-restricting cone. Subjects carried out the test in a darkened room.

B. Laptop screen showing the randomly placed dots around the vertical line (rod) that subjects have to set up to vertical with a roller mouse (details in [5]). The task is carried out both with the background dots stationary and with dots rotating around the line of sight clockwise and counter-clockwise (arrow) at 30deg/s. Visually induced rod tilt was used as a measure of visual dependence, calculated as the mean absolute rod tilt (in degrees) during disk rotation minus rod tilt values in the static condition[4].

C. Symptomatic recovery as measured by the dizziness handicap inventory (DHI) at the acute, recovery (10Week), and long-term recovery (10Month) phases. DHI values are normalised from 0-4. Error bars are Standard Error of the Mean.

D. Caloric canal paresis recovery. Most of the clinical (DHI) and caloric recovery takes place during the first 10 weeks. Despite this, individual clinical recovery is predicted by visual dependence rather than caloric improvement (see text).

Table 1

A. Matrix showing bivariate correlations between symptom recovery (DHI at 10 weeks) and acute psychophysical (threshold and supra-threshold tasks), canal paresis, visual dependency, and psychological variables.

			Acute										
				Supra-threshold		Threshold							
		Age (years)	Canal Paresis (%)	Perception Mean	Perception asymmetry (%)	Perception Mean	Perception asymmetry (%)	Visual Dependency	Static rod tilt	HADS	BSQ	VSS_A
DHI Recovery (10Week)	Pearson Correlation	0.233	-0.239	-0.059	-0.172	0.066	0.057	**0.504**	0.252	0.176	**0.351**†	**0.529**
	Sig. (2-tailed)	0.199	0.195	0.762	0.39	0.727	0.771	0.006	0.187	0.336	0.049	0.002

B. Matrix showing bivariate correlations between symptom recovery (DHI at 10 weeks) and psychophysical (threshold and supra-threshold tasks), canal paresis, visual dependency, and psychological variables also measured at 10 weeks (recovery stage).

			Recovery (10Week)									
				Supra-threshold		Threshold						
		Age (years)	Canal Paresis (%)	Perception Mean	Perception asymmetry (%)	Perception Mean	Perception asymmetry (%)	Visual Dependency	Static rod tilt	HADS	BSQ	VSS_A
DHI Recovery (10Week)	Pearson Correlation	0.233	**0.376**†	0.209	-0.093	**0.518**	-0.12	**0.556**	-0.115	**0.706**	**0.583**	**0.698**
	Sig. (2-tailed)	0.199	0.045	0.268	0.626	0.003	0.519	0.001	0.532	<0.001	0.001	<0.001

†Not significant after Larzelere and Mulaik adjusted Bonferroni test (Howell, 1992*)

*Howell, D. (1992). Statistical methods for psychology, (3rd Edition). Boston: PWS-Kent.

Table 2

Factor analysis summarising measures that correlate significantly (before adjustment) with symptomatic recovery (DHI at 10 weeks).

		Component[a]	
		1	2
		59% of variance	12% of variance
	Symptom score at recovery stage (DHI)	.71	
Acute	Visual Dependency	.72	
	Autonomic Arousal (VSS_A)	.89	
	Body Sensations Questionnaire	.75	
Recovery (10Week)	Vestibular Perceptual Threshold		.74
	Canal Paresis		.82
	Visual Dependency	.84	
	Hospital Anxiety & Depression Scale	.74	
	Body Sensations Questionnaire	.71	
	Autonomic Arousal (VSS_A)	.88	

[a] Component 1 accounts for 59% of variance within the data set, and component 2 accounts for 12% of variance. For clarity those variables that load strongly (>0.7, Hair et al., 1998*) on each component are shown only.

*Hair, J.F. Jr., Anderson, R.E., Tatham, R.L., & Black, W.C. Multivariate Data Analysis, (5th Edition). Upper Saddle River, NJ: Prentice Hall; 1998.