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Vestibulo-ocular function in anxiety disorders

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Abstract. Previous studies of vestibulo-ocular function in patients with anxiety disorders have suggested a higher prevalence of peripheral vestibular dysfunction compared to control populations, especially in panic disorder with agoraphobia. Also, our recent companion studies have indicated abnormalities in postural control in patients with anxiety disorders who report a high degree of space and motion discomfort. The aim of the present study was to assess the VOR, including the semicircular canal-ocular reflex, the otolith-ocular reflex, and semicircular canal-otolith interaction, in a well-defined group of patients with anxiety disorders. The study included 72 patients with anxiety disorders (age 30.6 $+/-$ 10.6 yrs; 60 (83.3%) F) and 29 psychiatrically normal controls (age 35.0 $+/-$ 11.6 yrs; 24 (82.8%) F). 25 patients had panic disorder; 47 patients had non-panic anxiety. Patients were further categorized based on the presence (45 of 72) or absence (27 of 72) of height phobia and the presence (27 of 72) or absence (45 of 72) of excessive space and motion discomfort (SMD). Sinusoidal and constant velocity earth-vertical axis rotation (EVAR) was used to assess the semicircular canal-ocular reflex. Constant velocity off-vertical axis rotation (OVAR) was used to assess both the otolith-ocular reflex and static semicircular canal-otolith interaction. Sinusoidal OVAR was used to assess dynamic semicircular canal-otolith interaction. The eye movement response to rotation was measured using bitemporal electro-oculography. Results showed a significantly higher VOR gain and a significantly shorter VOR time constant in anxiety patients. The effect of anxiety on VOR gain was significantly greater in patients without SMD as compared to those with SMD. Anxiety patients without height phobia had a larger OVAR modulation. We postulate that in patients with anxiety, there is increased vestibular sensitivity and impaired velocity storage. Excessive SMD and height phobia seem to have a mitigating effect on abnormal vestibular sensitivity, possibly via a down-weighting of central vestibular pathways.

Keywords: Space and motion discomfort, off-vertical axis rotation, height phobia

1. Introduction

Patients with vestibular dysfunction have an increased prevalence of clinical anxiety disorders [7,8,11, 14,15,18,30,31], and conversely, an increased prevalence of vestibular dysfunction has been found in certain anxiety disorders, particularly panic disorder with agoraphobia [19,26,34,36]. With few exceptions, however, previous studies of anxiety patients have regarded 'vestibular dysfunction' as a global clinical concept based on normal or abnormal results from a battery of clinical vestibular tests and have not considered specific physiological aspects of vestibular processing. Moreover, clinical vestibular testing, using standard measures such as caloric testing and earth-vertical axis rotational (EVAR) testing, has focused on the horizontal semicircular canal-ocular reflex. For example, in a previous study in our laboratory we found that patients with agoraphobia had an increased prevalence of unilaterally reduced vestibular response on caloric testing [19]. The few studies that have examined specific aspects of vestibular processing rather than clinical measures have focused on the vestibulo-spinal reflex [20,21]. However, Swinson, et al. [33], reported a significant increase in vestibulo-ocular reflex (VOR)

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gain in patients with panic disorder despite an otherwise negative study. Yardley et al. [36] reported abnormal posturographic findings in patients with panic disorder but reported no changes in VOR gain. A theme of previous findings in our laboratory has been that vestibular dysfunction is associated with specific aspects of anxiety disorder symptomatology, such as 1) agoraphobia, 2) dizziness when not anxious, and 3) Space and Motion Discomfort (SMD) [19], i.e., a profile of symptom-eliciting situations seen in both patients with anxiety disorders and patients with vestibular disorders [22]. Among the diverse situations that elicit SMD, certain ones, including 'looking up at tall buildings', 'closing eyes in the shower', and 'leaning far back in a chair' suggest otolith involvement. Despite this evidence suggesting a possible otolithic abnormality in patients with panic disorder, no previous study has examined otolith-ocular function.

The present study was undertaken as part of a broad research enterprise that aimed at 1) further studying anxiety disorder symptom correlates of vestibular dysfunction and 2) examining what aspects of vestibular processing are particularly affected in anxiety disorders. The symptom correlates of interest included 1) the presence or absence of panic disorder, 2) the presence or absence of height phobia, and 3) the presence or absence of excessive SMD. Height phobia was of particular interest because previous studies suggested that postural control may be altered upon exposure to heights both in normal subjects [1,3,6,17] and in patients with height phobia [25]. In our larger overall study, we analyzed 1) clinical vestibular responses, 2) sensory integration in the maintenance of upright balance, and 3) details of the VOR including the otolith-ocular reflex and semicircular canal-otolith interaction. In this paper we report the lattermost, i.e., VOR, findings.

2. Methods

Enrollment in this study, which included psychiatric assessments and vestibulo-ocular testing, was performed with the consent of each subject based upon a protocol and consent form approved by the Institutional Review Board at the University of Pittsburgh.

Subjects included psychiatric patients with a primary diagnosis of an anxiety disorder and psychiatrically normal controls between the ages of 18 and 55 years. Anxiety patients were included if they had panic disorder or "non-panic anxiety," which typically consisted of generalized anxiety disorder or social phobia. Also, subgroups were formed according to the presence or absence of height phobia and the presence or absence of excessive space and motion discomfort (SMD) as follows: Height phobia status (absent vs present) was based on: 1) clinician-rated fear of height on a scale of 0–8 ("no fear" to "very severe fear"), and 2) clinician-rated avoidance of heights on a scale of 0–8 ("no avoidance" to "always avoid") from the "Specific Phobia" section of the ADIS [5]. To be accepted as a normal control or as an anxiety patient without fear of height, individuals had to have zero ratings on both fear and avoidance of heights. Anxiety patients with non-zero fear and avoidance ratings indicating a mild severity level (3 or less on both scales) were omitted for analysis of height phobia. The remaining anxious phobic subjects; i.e., those with a severity level of 4 or more on either the fear or avoidance of heights scale were considered height phobic. Subjects were categorized as having excessively high SMD if their score on the SMD-1 subscale of the Situational Characteristics Questionnaire [22] was greater than or equal to 6.5. The cutoff of 6.5 was based upon the normal subject data (see Table 1). The study included 72 anxiety patients (age 30.6 $+/-$ 10.6 yrs; 60 (83.3%) F) and 29 psychiatrically normal controls (age 35.0 $+/-$ 11.6 yrs; 24 (82.8%) F). Twenty-five patients had panic disorder; 47 patients had non-panic anxiety. 40 of 72 patients had height phobia and 25 had no fear of heights. Twenty seven of 72 patients had excessive SMD. No control subject had height phobia or excessive SMD. Patients could not have taken benzodiazepine type medication within 2 weeks of the vestibular assessment. Antidepressant medication was permitted if the dose was kept constant. Participants could not have a history of substance abuse, obsessive compulsive disorder or psychotic disorder. Furthermore, individuals with active migraine, or a history of head injury were excluded. Patients were recruited from a psychiatric outpatient clinic setting. Patients were first examined with standard clinical psychiatric assessments. Potentially eligible subjects were examined further using a structured diagnostic interview focused on anxiety disorders, i.e., the Anxiety Disorders Interview Schedule [5].

Vestibular testing consisted of yaw earth-vertical axis rotation (EVAR) to assess the horizontal semicircular canal-ocular reflex and yaw off-vertical axis rotation (OVAR) to assess the otolith-ocular reflex and dynamic otolith-semicircular canal interaction. Yaw OVAR is thought to stimulate primarily the utricles as they lie approximately in the head-horizontal, i.e., yaw, plane.

Table 1
Characteristics of the subjects

	Normal SMD	Abnormal SMD
Control subjects ($n = 29$)	29	0
Non-panic anxiety patients ($n = 47$)	29 (14 w/ height phobia)	18 (10 w/ height phobia)
Panic patients ($n = 25$)	16 (7 w/ height phobia)	9 (8 w/ height phobia)

Additionally, post-rotational responses following the cessation of constant velocity OVAR were recorded to assess static otolith-semicircular canal interaction. EVAR consisted of sinusoidal testing at 0.02, 0.05, and 0.1 Hz at a peak velocity of 50/deg/sec and constant velocity at 60 deg/sec both clockwise and counterclockwise. For constant velocity rotation, subjects were rotated until vestibulo-ocular responses decayed to a negligible level and then immediately decelerated at 100/deg/sec/sec to a stop. All vestibular testing was performed with eyes opened in the dark. Constant velocity OVAR, which was performed after EVAR, used a rotate-then-tilt paradigm at a constant velocity of 60/deg/sec with an off-vertical tilt of 30 degrees. OVAR was performed in only one direction to minimize the nausea produced by the stimulus. Per-rotatory constant velocity responses while tilted were used to assess the otolith-ocular reflex independent of the semicircular canal-ocular reflex. OVAR was stopped using a deceleration of 100 deg/sec/sec such that the subject's position was nose-up when they stopped rotating. Responses following cessation of constant velocity OVAR were used to assess static otolith-semicircular canal interaction. Sinusoidal OVAR at the same frequencies and amplitude used for sinusoidal EVAR was used to assess dynamic otolith-semicircular canal interaction. To assess anxiety levels during vestibular testing, patients completed the Spielberger State Anxiety Inventory [29] at baseline, after EVAR and after OVAR.

The eye movement response to rotation was measured using bitemporal electro-oculography using standard techniques. Electro-oculographic signals were digitized at 100 Hz and processed off-line. Eye movement analysis consisted of an automated computer algorithm that separated fast and slow components of vestibular nystagmus so that the slow component velocity of the eye movement response to rotation could be assessed. For sinusoidal responses to both EVAR and OVAR, gain, phase, and symmetry were computed using standard methods. The responses to constant velocity EVAR were used to compute the magnitude and time constant of the exponential slow component eye velocity response. A similar technique was used to analyze responses following the cessation of constant velocity OVAR. For per-rotatory constant velocity OVAR responses, the bias and modulation components were computed using standard techniques.

Statistical analyses consisted of ANOVA. For sinusoidal responses, gain, phase, and symmetry were analyzed separately using full-factorial ANOVA's with independent variables being the type of rotation (EVAR, OVAR) and frequency (0.02 Hz, 0.05 Hz, 0.1 Hz), both within-subject factors, and group membership as a between-subject factor. For each of gain, phase, and symmetry, four different full-factorial ANOVA's were performed for group membership designations as follows: 1) anxiety vs. controls; 2) panic disorder vs. non-panic anxiety vs. controls; 3) anxiety with height phobia vs. anxiety without height phobia vs. controls; and 4) anxiety with excessive SMD vs. anxiety without excessive SMD vs. controls. For post-rotatory responses, gain and time constant were analyzed separately using four full-factorial ANOVA's for each response parameter with the type of rotation (EVAR, OVAR) as a within-subject factor and group membership as a between-subject factor. Group membership designations for post-rotatory responses were the same as those used for sinusoidal responses. For per-rotatory OVAR responses, i.e., modulation component and bias component, we used group membership as a single, between-subject, factor. Post-hoc comparisons were performed when appropriate. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Sinusoidal responses

Vestibulo-ocular responses for sinusoidal EVAR are shown in Table 2A and for sinusoidal OVAR are shown in Table 3A. Analysis of gain during sinusoidal responses revealed main effects of group ($p = 0.01$) and frequency ($p < 0.0001$), with no significant main effect of type of rotation when comparing patients overall to controls. There were no significant interactions between group and any of the within-subject factors. Patients had a higher gain than controls. There were no significant differences between anxiety patients and control subjects with respect to phase or symmetry. The

Table 2
Earth-Vertical Axis Rotation Responses in Patients with Anxiety Disorders. Values are mean $+/-$ one standard deviation

A. Per-rotatory Responses for Sinusoidal Rotations									
	0.02 Hz			0.05 Hz			0.1 Hz		
	Gain	Phase (°)	Symmetry (°/sec)	Gain	Phase (°)	Symmetry (°/sec)	Gain	Phase (°)	Symmetry (°/sec)
Anxiety Patients	0.44 ± 0.12	21.7 ± 6.3	1.7 ± 1.4	0.56 ± 0.14	8.6 ± 4.6	2.2 ± 1.7	0.54 ± 0.16	3.0 ± 4.4	2.0 ± 1.4
Control subjects	0.41 ± 0.13	19.7 ± 7.0	1.5 ± 1.4	0.49 ± 0.17	7.6 ± 5.6	2.0 ± 1.2	0.50 ± 0.17	2.5 ± 4.4	1.9 ± 1.2
B. Post-rotatory Responses for Constant Velocity Rotations									
	Gain	Time Constant (°)							
Anxiety Patients	0.58 ± 0.17	21.4 ± 6.4							
Control subjects	0.56 ± 0.14	24.2 ± 8.5							

Table 3
Off-Vertical Axis Rotation Responses in Patients with Anxiety Disorders. Values are mean $+/-$ one standard deviation

A. Per-rotatory Responses for Sinusoidal Rotations									
	0.02 Hz			0.05 Hz			0.1 Hz		
	Gain	Phase (°)	Symmetry (°/sec)	Gain	Phase (°)	Symmetry (°/sec)	Gain	Phase (°)	Symmetry (°/sec)
Anxiety Patients	0.42 ± 0.11	22.8 ± 5.9	1.6 ± 1.2	0.56 ± 0.17	11.0 ± 4.2	1.7 ± 1.3	0.61 ± 0.18	8.5 ± 4.7	1.6 ± 1.5
Control subjects	0.41 ± 0.13	22.1 ± 6.6	1.2 ± 1.0	0.53 ± 0.16	10.3 ± 4.1	1.2 ± 0.8	0.56 ± 0.17	8.7 ± 4.1	2.0 ± 1.1
B. Post-rotatory Responses for Constant Velocity Rotations									
	Gain	Time Constant (°)							
Patients	0.40 ± 0.17	10.2 ± 4.0							
Control subjects	0.39 ± 0.15	13.7 ± 4.9							
C. Per-rotatory Responses for Constant Velocity Rotations									
	Modulation (°/sec)	Bias (°/sec)							
Patients	7.1 ± 4.9	2.7 ± 4.4							
Control subjects	6.5 ± 2.9	3.8 ± 3.8							

type of anxiety diagnosis (panic versus no panic) was not a significant factor for gain, phase, or symmetry. The presence or absence of height phobia was not a significant factor for gain, phase, or symmetry. Gain was significantly associated with level of SMD ($p = 0.01$) (Fig. 1). Patients without excessive SMD had a higher gain than that in controls ($p = 0.02$) and patients with excessive SMD had a gain that did not differ from that in controls. Patients without excessive SMD had a trend toward higher gain compared to patients with excessive SMD ($p = 0.07$). The presence or absence of excessive SMD was not a significant factor for phase or symmetry.

3.2. Post-rotatory responses

Post-rotatory responses for constant velocity EVAR are given in Table 2B and for constant velocity OVAR in table 3B. Analysis of the time constant revealed a significant effect of both type of rotation ($p < 0.0001$) and group membership ($p = 0.002$) when comparing patients overall to controls. There were no significant interactions between group and any of the within-subject factors. The time constant was smaller, i.e., the post-rotatory nystagmus lasted for a shorter amount of time, in the patient group compared with controls and was smaller for OVAR compared with EVAR. The type of anxiety diagnosis, i.e. the presence or absence of panic disorder, the presence or absence of height phobia, and the presence or absence of excessive SMD were not significant factors for time constant. There were no significant effects for gain for constant velocity responses.

3.3. Per-rotatory otolith-ocular responses

Per-rotatory otolith-ocular responses during constant velocity OVAR are given in Table 3C. There were no statistically significant effects found for either the modulation or the bias component for anxiety overall, type of anxiety diagnosis, or the presence or absence of SMD. However, for the modulation component, which

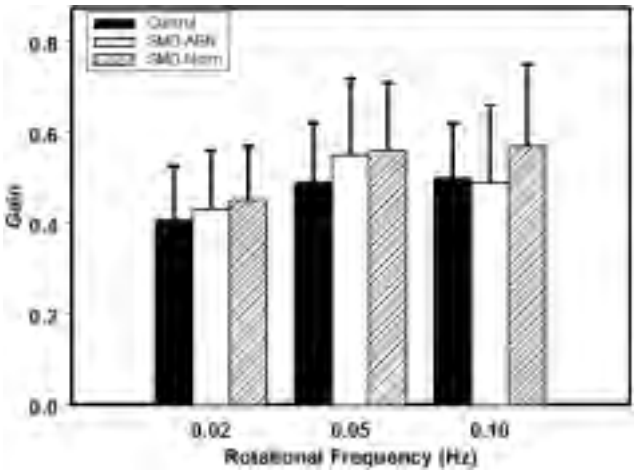

Fig. 1. Vestibulo-ocular reflex gain in anxiety patients with (SMD-ABN) and without (SMD-Norm) excessive space and motion discomfort (SMD). Data are shown for three rotational frequencies, i.e., 0.02 Hz, 0.05 Hz, and 1.0 Hz. Data from non-anxious control subjects (Control) are shown for comparison. Error bars represent one standard deviation.

reflects the direct otolith-ocular reflex, there was a significant effect of height phobia ($p = 0.02$); Anxious patients without height phobia had a larger modulation component than either height phobics or controls. The modulation component was 8.9 deg/sec with a standard deviation of 5.4 deg/sec in the non-height phobic patients, 5.6 $+/-$ 3.7 deg/sec in the height phobics, and 6.5 $+/-$ 3.0 deg/sec in the controls. There was no effect of height phobia on the bias component.

3.4. Anxiety during rotational testing

We analyzed the state anxiety data to determine whether there were differential effects of rotational testing on the anxiety level of patients vs. controls. As expected, there was a higher baseline anxiety in the patients as compared with controls. Furthermore, anxiety levels were increased both during EVAR and during OVAR. However, the amount of increase in anxiety above baseline did not differ between patients and controls. Also, the increase in anxiety did not differ between patients with panic disorder vs. those with non-panic anxiety, between patients with height phobia vs. those without height phobia, or between patients with excessive SMD vs. those without excessive SMD.

4. Discussion

This study assessed vestibulo-ocular responses in patients with anxiety disorders including panic disorder and non-panic anxiety. The influence of height phobia and SMD (space and motion discomfort) also was assessed. There were statistically significant differences between anxiety patients and controls regarding the gain of the semicircular canal-ocular reflex. This finding replicates that of Swinson et al. [33] who studied patients with panic disorder. We also found a decreased VOR time constant in patients with anxiety. No differences were found for VOR asymmetry, the otolith-ocular reflex, or semicircular canal-otolith interaction.

The combination of increased gain and shorter time constant is not typical of most vestibular disorders. For example, in peripheral vestibular disease, although the VOR time constant is shorter, VOR gain is decreased [23]. In central vestibular disorders, gain may be abnormally large, such as in patients with vestibulo-cerebellar lesions [35] and migraine-related dizziness [12], but the time constants are not shorter. In vestibulo-cerebellar disease, gain is elevated and the VOR time constant is lengthened. Thus, the combination of increased gain and decreased time constant in anxiety may represent an identifiable pattern of changes in the VOR.

Our results are unlikely to have been based on a generalized arousal effect [9] since an increase in semicircular canal-ocular reflex gain was not accompanied by comparable changes in other VOR parameters such as otolith-ocular reflex gain. Also, the VOR time constant was shorter in patients, not longer, as might be expected with increased arousal [13]. Furthermore, in both this study and in an earlier study [19], we found no differential increase in state anxiety during vestibular testing in patients vs. control subjects.

We found a rather complex interaction between space and motion discomfort (SMD) and the increased VOR gain associated with anxiety. Within the group of patients with anxiety, those with excessive SMD had decreased VOR gain as compared to those without excessive SMD. Thus, anxious patients with excessive SMD did not reach the gain they would have reached had they not had excessive SMD. We propose that this effect is a general "down-weighting" of vestibular signals by the CNS. In a previous study, which used computerized dynamic posturography, we found that anxious patients with excessive SMD adopt a sensory processing style that is consistent with both visual and somatosensory dependence [20,21], i.e., a down-weighting of vestibular signals compared to visual and somatosensory signals. A parallel study of optic flow sensitivity during standing balance in the patients examined here confirms a relative up-weighting of visual signals in patients with excessive SMD, but not in patients with height phobia [27]. Thus, the vestibulo-ocular findings from the present study and our previous findings regarding vestibulo-spinal and visuo-spinal responses are consistent with the supposition that anxious patients with SMD down-weight their vestibular responses as compared with anxious patients without excessive SMD. Our data also show a similar effect regarding patients with height phobia and OVAR modulation. That is, anxious patients with height phobia did not reach the same large modulation component that they would have reached had they not had height phobia. Comparable to the argument above regarding SMD, we propose that patients with height phobia have a general down-weighting of vestibular signals in the CNS. The basis for this relative inhibition of vestibular signals in patients with excessive SMD and in patients with height phobia is uncertain. However, a candidate location for this effect may be the cerebral cortex wherein sensory-sensory inhibition is well described [2,4,10, 32]. Reduced vestibular sensitivity in patients with SMD and in patients with height phobia may underlie their abnormal postural control by interfering with the appropriate weighting of sensory signals important for balance [24].

The pathophysiology of increased gain of the semicircular canal-ocular reflex in anxiety might have a neurochemical basis. Noradrenergic and/or serotonergic pathways via the locus coeruleus and dorsal raphe nuclei to the vestibular nuclei [16,28] may have influenced the VOR, but note that the modulation component of the otolith-ocular reflex was not similarly increased. Possibly, there is a differential effect of monoaminergic modulation on canal-ocular versus otolith-ocular pathways. The dynamics of the VOR were slightly impaired as evidenced by a short VOR time constant, suggesting a reduction in the efficacy of velocity storage. The pathophysiological basis of this finding is uncertain but also may be neurochemical. Our finding of altered VOR gain is comparable to recently reported changes in the sensitivity of the VOR of patients with migraine-related dizziness [12], which also may be a disorder of monoaminergic function.

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