Contribution of intravestibular sensory conflict to motion sickness and dizziness in migraine disorders

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Wang J. Lewis RF. Contribution of intravestibular sensory conflict to motion sickness and dizziness in migraine disorders. J Neurophysiol 116: 1586–1591, 2016. First published July 6, 2016; doi:10.1152/jn.00345.2016.—Migraine is associated with enhanced motion sickness susceptibility and can cause episodic vertigo (vestibular migraine (VM)), but the mechanisms relating migraine to these vestibular symptoms remain uncertain. We tested the hypothesis that the central integration of rotational cues (from the semicircular canals) and gravitational cues (from the otolith organs) is abnormal in migraine patients. A postrotational tilt paradigm generated a conflict between canal cues (which indicate the head is rotating) and otolith cues (which indicate the head is tilted and stationary), and eye movements were measured to quantify two behaviors that are thought to minimize this conflict: suppression and reorientation of the central angular velocity signal, evidenced by attenuation (“dumping”) of the vestibulocular reflex and shifting of the rotational axis of the vestibulocular reflex toward the earth vertical. We found that normal and migraine subjects, but not VM patients, displayed an inverse correlation between the extent of dumping and the size of the axis shift such that the net “conflict resolution” mediated through these two mechanisms approached an optimal value and that the residual sensory conflict in VM patients (but not migraine or normal subjects) correlated with motion sickness susceptibility. Our findings suggest that the brain normally controls the dynamic and spatial characteristics of central vestibular signals to minimize intravestibular sensory conflict and that this process is disrupted in VM, which may be responsible for the enhanced motion intolerance and episodic vertigo that characterize this disorder.

vestibular; migraine; motion sickness; vertigo; eye movements

NEW & NOTEWORTHY

The present study examines the relationship between migraine, motion sickness, and vertigo and the mechanisms used by the brain to resolve conflict between the two types of vestibular information provided by the labyrinth (semicircular canals and otolith organs). We demonstrate specific differences in eye movement responses between normal and migraine subjects when tested with a motion paradigm that generates canal-otolith conflict and interpret these findings in the context of normal and aberrant processing in the vestibulocerebellum.

MIGRAINE is characterized by increased sensitivity to sensory stimuli (Harriott and Schwedt 2014) and can cause a variety of neurologic symptoms, including episodic vertigo [vestibular migraine (VM)] (Neuhauser et al. 2006). Enhanced susceptibility to motion sickness is also associated with migraine, but VM patients experience more pronounced motion sickness than migraine patients who lack episodic dizziness (Jeong et al. 2010). The confluence of migraine, vertigo, and motion sickness in VM is intriguing because it suggests possible shared or overlapping pathophysiology. Specifically, VM patients have episodic vertigo that is often positional (provoked or exacerbated by tilting the head relative to gravity) (Kayan and Hood 1984), and positional nystagmus is commonly observed in VM patients during vertigo episodes (Polensk and Tusa 2009). Reorienting the head relative to gravity modulates activity in the semicircular canals, which encode angular head velocity, and otolith organs, which encode gravity and linear acceleration. Based on these observations, we proposed that central integration of canal and otolith signals is abnormal in VM, a hypothesis supported by our recent psychophysical studies (Lewis et al. 2011a, 2011b; Wang and Lewis 2016).

Motion sickness is theorized to result from conflict between sensory signals or between anticipated and actual sensory inputs, where “conflict” implies a signal combination that violates habitually experienced patterns (Oman 1990; Yates et al. 1998). This conflict can be between senses (e.g., visual and vestibular) or within a sense (e.g., between canal and otolith signals). Furthermore, motion sickness requires peripheral vestibular function (Money 1970) and may also depend on the cerebellar nodulus/uvula (Wang and Chinn 1956), the brain region where canal and otolith signals are synthesized (Angelaki et al. 2010). Taken together, these observations suggest that aberrant canal-otolith integration could contribute to the enhanced motion sickness susceptibility observed in migraine and VM.

To examine the hypothesis that abnormalities in central canal-otolith integration contribute to both episodic dizziness and motion intolerance in migraine disorders, we tested VM, migraine, and normal subjects with a postrotational tilt paradigm that induces a canal-otolith conflict and measured eye movements to characterize the brain’s response to this pattern of vestibular stimuli (Angelaki and Hess 1994). Subjects were rotated at a constant velocity about an earth vertical axis until the vestibular response resolved, rapidly decelerated to a stop (generating an angular velocity signal directed opposite to the prior rotation), and then tilted away from upright. After tilting, the brain received an angular velocity signal from the canals (although the head was stationary) and a static tilt signal from the otolith organs, and these inputs conflict because rotation about a tilted axis should produce dynamic modulations in otolith inputs. Eye movements display two characteristic re-
sponses to this paradigm; the postrotational vestibulococular reflex (VOR) is attenuated (“dumping”) and the eye’s rotational axis shifts toward gravity (“spatial orientation”) (Cohen et al. 1999). VM patients demonstrated several abnormalities when tested with this paradigm, suggesting their resolution of canal-otolith conflict differs from migraine and normal subjects, and we propose that these differences relate to the enhanced motion sensitivity and episodic vestibular symptoms observed in VM.

MATERIALS AND METHODS

This study was approved by the hospital’s Institutional Review Board, and each subject provided written informed consent.

Subjects. Ten VM, migraine, and normal subjects were studied. All subjects lacked a history of other neurological or otological disease, were not on migraine prophylactic medications, and had not experienced a migraine or dizziness episode within 2 wk of testing. VM subjects met the currently accepted clinical criteria for definite VM (Lempert et al. 2012) and had normal physical exams, audigrams, brain MRIs, and vestibular testing (bithermal caloric and sinusoidal rotational testing). Migraine subjects met International Headache Society criteria for migraine without aura (Headache Classification Subcommittee 2004), had no vestibular symptoms, and had normal brain MRIs and vestibular testing. Normal subjects had no history of migraine or vestibular symptoms and had normal vestibular testing. Motion sickness sensitivity was quantified with the revised Golding questionnaire (Golding 1998).

Testing protocol. Subjects sat in a padded chair in complete darkness and were restrained with a harness, and their head was immobilized in the upright orientation with its center aligned with the earth vertical yaw rotational axis. They were accelerated about this rotational axis at 120°·s$^{-1}$ toward their right (clockwise when viewed from above) over 1 s, maintained at a constant angular velocity of 120°/s for 90 s, and then symmetrically decelerated to a stop (Fig. 1, C and D) and fitting a regression line to the SPV beginning when the axis shift was maximal. The VOR axis shift was defined as the angle between the upright y-axis and the SPV regression line and was therefore 0° (aligned with the earth vertical) for a purely horizontal rotation and 90° (aligned with the earth horizontal) for a purely vertical rotation.

Two parameters were calculated from the time constant and axis data, both of which were normalized so that a value of zero indicated no compensation to the sensory conflict generated by the paradigm and a value of unity indicated complete resolution of the sensory conflict. The axis index (AI) was defined as the [axis shift(tilted) − axis shift(upright)/45°]; if the eye’s rotational axis shifted by a magnitude equal to the size of the head tilt (e.g., aligned with gravity), then the brain would interpret the rotational cue as occurring about an earth vertical axis that resolved the sensory conflict. The dumping index (DI) was calculated using the postrotatory VOR time constant in the upright and tilted conditions as [time constant(upright) − time constant(tilted)/T$_{10}$1(upright)]; if tilting the head had no effect on the time constant, then the DI was zero, but if it totally eliminated the postrotatory VOR response (by completely suppressing the brain’s angular velocity signal and thereby resolving the sensory conflict), then its value was unity. Although dumping works by discharging velocity storage (Waespe et al. 1985) and therefore cannot reduce the VOR time constant below that of the afferent input (∼6 s), the DI was defined based on the extent of optimal conflict resolution rather than the extent of optimal dumping. Analysis using the latter approach had no effect on the results except for increasing DI values for all subjects, which did not alter the pattern of findings and therefore is not presented below.

RESULTS

Overview. Figure 1 shows eye movement responses in a normal subject. During rotation, a horizontal VOR response was generated, which decayed with a time constant between 15 and 20 s and no meaningful vertical VOR response occurred (Fig. 1, A and B). After the head decelerated to a stop, if the head remained upright (Fig. 1A), then the postrotatory VOR closely mirrored the per-rotatory response, as the horizontal component decayed with a similar time constant (19.1 s in this example) and essentially no vertical VOR response occurred. When plotted in polar coordinates (Fig. 1C), trials with the head upright were characterized by a rise and fall in horizontal eye velocity along the y-axis, with minimal vertical eye velocity displacement along the x-axis, and a line fit to the eye velocity trace was nearly aligned with the y-axis (e.g., the axis shift was 2.0°). When the head was tilted in roll by 45° after deceleration to a stop (Fig. 1B), the postrotatory horizontal VOR was attenuated (time constant of 12.3 s in this example) and a vertical VOR response was generated. When plotted in polar coordinates (Fig. 1D), the vertical VOR component shifted the eye velocity trace away from the y-axis, and it decayed toward the origin along a line that was tilted toward the alignment of gravity (axis shift of 27.6°). For this subject, therefore, the AI was $(27.6 - 2.0)/45 = 0.57$ and the DI was $(19.1 - 12.3)/19.1 = 0.36$.

Magnitude of eye movement and motion sickness parameters. Figure 2 shows the means (+1SE) for the normal, migraine, and VM subjects for each of the measured parameters. Subjects differed significantly only for motion sickness susceptibility [by motion sickness susceptibility questionnaire (MSSQ)] and the AI: in both cases, VM patients had significantly larger means than migraine or normal subjects, whereas the latter two groups did not differ [MSSQ: VM/migraine
patients, \( P = 0.04 \) by Mann-Whitney test; VM/normal patients, \( P = 0.01 \) by Mann-Whitney test; migraine/normal patients, \( P = 0.49 \) by Mann-Whitney test; ANOVA (on ranks) for the three groups: \( P = 0.02 \); and AI: VM/migraine patients, \( P = 0.007 \) by \( t \)-test; VM/normal patients, \( P = 0.02 \) by Mann-Whitney test; migraine/normal patients, \( P = 0.38 \) by \( t \)-test; ANOVA (Holm-Sidak) for the three groups: \( P = 0.04 \). Motion sickness susceptibility did not correlate with the VOR time constant, AI, or DI in any of the three subject groups (Pearson \( R \), \( P > 0.05 \) for all comparisons).

Relationship between the axis shift and dumping. Figure 3 shows the normalized axis shift (AI) plotted against the normalized dumping efficacy (DI) for the three subject groups. If we consider the AI as the fraction of the sensory conflict resolved with the axis shift and the DI as the fraction resolved by dumping, then if the brain controlled their relative amplitudes to optimize the resolution of sensory conflict, data points would fall on the line \( (\text{AI} + \text{DI}) = 1 \), which are the solid lines in Fig. 3. As shown in Fig. 3, individual AI and DI values for normal and migraine subjects were highly correlated and fell close to this line, which had a slope of \(-1.0\) and \( x \)- and \( y \)-intercepts of \( +1.0 \); linear regression for normal subjects \( (P = 0.02, R = 0.74) \) had a slope of \(-0.9\) with \( y \)- and \( x \)-intercepts of \( 0.82 \) and \( 0.91 \); and linear regression for migraine subjects \( (P = 0.03, R = 0.63) \) had a slope is \(-1.04\) with \( y \)- and \( x \)-intercepts of \( 0.87 \) and \( 0.84 \). VM patients deviated from this pattern, as their data showed no correlation between AI and DI values with linear regression \( (P = 0.43, R = 0.28) \).
having a slope of 0.16 and a y-intercept of 0.61. Slopes of the regression lines did not differ between normal and migraine subjects \( [P = 0.38 \text{ by analysis of covariance (ANCOVA)}] \) but were significantly different for VM subjects compared with normal or migraine subjects \( (P < 0.001 \text{ for each comparison by ANCOVA}) \). Since the \( (AI + DI = 1) \) line can be considered the location of optimal conflict resolution, we defined the “residual conflict” value for each subject as the distance of their data point from this line, which equals (for subject \( i \)) the absolute value of \( [1 - (AI + DI)]/2 \). Residual conflict values were larger in the VM group than in other groups, but this difference was not significant \( (\text{means} \pm \text{SE}; \text{VM group: } 0.16 \pm 0.04, \text{migraine group: } 0.11 \pm 0.02, \text{and normal group: } 0.12 \pm 0.02; P = 0.28 \text{ by t-test}) \). In the VM group but not the normal or migraine groups, however, residual conflict values were correlated significantly with motion sickness susceptibility scores \( (\text{linear regression: } P = 0.03 \text{ for MSSQ/residual error correlation with a slope of 37.7 in the VM group; correlations were } > 0.36 \text{ for the migraine and normal groups}) \).

**DISCUSSION**

The mechanisms underlying vestibular symptomatology associated with migraine, including episodic dizziness and enhanced motion sickness susceptibility, are uncertain \( \text{(Casini et al. 2009; Furman et al. 2013)} \). In the present study, we examined eye movement responses in VM, migraine, and normal subjects using a motion paradigm that generates conflict between canal and otolith signals and found that eye movement responses in VM patients differed from migraine and normal subjects in three ways: the VOR axis shifts were larger in VM patients, the AI and DI were not correlated in VM patients, and the residual conflict in VM patients was positively correlated with motion sickness susceptibility. Below, we discuss these results in the context of intravestibular sensory conflict and its resolution and propose that VM subjects demonstrate aberrant resolution of canal-otolith conflict, which could relate directly to both their enhanced motion intolerance and episodic vertigo.

**Axis shift.** VM patients had larger axis shifts after postrotational tilts than migraine or normal subjects. Since the eye’s rotational axis is thought to indicate the brain’s estimated orientation of gravity relative to the head \( \text{(Cohen et al. 1999)} \), the larger axis shift in VM patients implies an abnormal overestimate of the amplitude of the roll head tilt compared with the control groups \( \text{(although it was still smaller than the actual head tilt)} \). This observation is consistent with our prior findings that roll tilt perceptual thresholds are reduced in VM relative to controls \( \text{(Lewis et al. 2011a, 2011b)} \), as both are evidence of an abnormally sensitized response to the coplanar roll canal and otolith cues that are present during roll head tilts. We previously suggested that this may reflect dysfunction in the cerebellar nodulus and uvula \( \text{(since canal and otolith signals are first integrated there)} \) \( \text{(Angelaki et al. 2010)} \) or its projections to the vestibular nuclei. Although our prior perceptual studies suggested that vestibular-only (VO) neurons in the vestibular nuclei, which project rostrally to the thalamus \( \text{(Meng et al. 2007)} \), are a source of this aberrant information in VM \( \text{(Russo et al. 2014)} \), our current oculomotor results imply that the neurons in the vestibular nuclei that project into VOR pathways \( \text[projection-vestibular-pause (PVP) neurons and/or floccular-target neurons (FTN) \text{(Cullen 2012) are also sources} \) \( \text{of this information. It is unclear, however, if VO and VOR interneurons receive these signals from the cerebellum or other anatomic loci or if this aberrant information is generated within vestibular nuclei. While the axis shift is mediated through the velocity storage integrator in the brain stem \( \text{(Whitney et al. 2015)} \), our findings do not simply reflect enhanced velocity storage in VM, since the horizontal VOR time constant \( \text{the most direct measure of velocity storage) was not prolonged in our VM cohort \text{although it was} \text{slightly increased in a much larger prior study, Jeong et al. 2010, nor did it correlate with motion sickness severity.}} \)

**Relationship between the VOR axis shift and dumping.** Although VOR dumping and axis shift behaviors have previously been described in frontal-eyed primates \( \text{monkeys and humans)} \) when tested with a postrotational tilt paradigm \( \text{(cf. Angelaki and Hess 1994; Zupan et al. 2000)} \), the variability between subjects has never been examined, and, hence, the relationship between these two features of the VOR has not been defined. At least three mechanisms could potentially control the relative amplitudes of the axis shift and dumping, but only one mechanism is consistent with our results in the normal and migraine subjects. First, it is clear that dumping is more complete for the postrotational tilt paradigm when the amplitude of the head tilt is larger \( \text{(Angelaki and Hess 1994)} \). It is therefore reasonable to postulate that the brain’s internal estimate of the head tilt would directly affect the extent of dumping, since the former presumably follows the amplitude of the physical head tilt. In this scenario, larger axis shifts \( \text{(which imply larger estimates of head tilt) should lead to more} \)

![A graph showing the relationship between axis index (AI) and dumping index (DI) for three subject groups: normal, migraine, and vestibular migraine.](image-url)
extensive dumping, the opposite of the pattern we observed. Second, the VOR axis is based on the relative magnitudes of the horizontal and vertical VOR responses and for the same-sized vertical response, the axis shift is larger when the horizontal component of the VOR is smaller. This analysis implies that more extensive dumping, which attenuates the horizontal VOR, would lead to an increase in the axis shift (Laurens and Angelaki 2011), which is again the opposite of the pattern we observed.

The axis shift and dumping can also be considered as two complementary mechanisms to resolve the sensory conflict produced by the postrotational tilt paradigm (Bockisch et al. 2003). With this scenario, the goal would be that the portion of conflict resolution accomplished by the axis shift and the portion accomplished by dumping should sum to an optimal value. Our results are consistent with a relatively simple implementation of this concept, since (AI + DI) values approximated unity for normal and migraine subjects and the two measures were inversely correlated. Our data therefore suggest that intravestibular sensory conflict is minimized by the brain by optimizing the axis shift and dumping features of the VOR in concert, although the mechanism(s) underlying the relative sizes of AI and DI values in an individual subject are uncertain.

VM subjects do not show the same inverse correlation between the AI and DI and therefore do not optimize the resolution of canal-otolith sensory conflict like the control groups. It is not clear why VM subjects do not demonstrate this correlation; it may be that they lack the mechanism that controls the relative extent of the axis shift and dumping in the presence of a canal-otolith conflict or they may have this mechanism but it could be nullified by one of the other potential mechanisms described above, which are associated with a positive correlation rather than a negative correlation between AI and DI values.

Relationship between canal-otolith sensory conflict and motion sickness. Unlike migraine and normal subjects, the residual sensory conflict for VM patients [e.g., the shortest distance on the AI-DI plot between the subject’s values and the optimal (AI + DI = 1) line] correlated with motion sickness susceptibility. This finding suggests that the enhanced motion intolerance experienced by VM subjects relates to the brain’s resolution of intravestibular sensory conflict, where “sensory” indicates either the actual sensory signals or the difference between the actual and predicted signals (Oman and Cullen 2014). While this concept has formed the basis of motion sickness theory, it is interesting that our analysis does not provide an explanation for the less severe motion intolerance suffered by normal and migraine subjects, only the enhanced motion susceptibility associated with VM. It may be that our paradigm and analysis are not adequately sensitive to identify a sensory conflict component to motion sickness in the non-VM groups or, more likely, that the motion sickness experienced by normal and migraine subjects is not directly due to the canal-otolith conflict we studied with the postrotational tilt paradigm but perhaps is more heavily weighted toward visual-vestibular or other forms of sensory conflict.

Conclusions. Our findings demonstrate that the brain normally controls the dynamic and spatial characteristics of the central vestibular signals (as reflected in the VOR response) to minimize intravestibular sensory conflict and that this process is disrupted in VM, leading to a number of eye movement abnormalities that are indicative of abnormal canal-otolith integration. These results, taken together with our prior psychophysical studies, suggest that the cerebellar nodulus/uvula functions abnormally in VM and that this dysfunction may be responsible for the motion intolerance and episodic vertigo that characterize this disorder.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES


