Published in final edited form as:

Exp Brain Res. 2010 July ; 204(2): 207–222. doi:10.1007/s00221-010-2305-4.

Motion sickness induced by off-vertical axis rotation (OVAR)

Mingjia Dai,

Department of Neurology, Mount Sinai School of Medicine, 1 East 100th Street, Box 1135, New York, NY 10029, USA

Sofronis Sofroniou,

Department of Neurology, Mount Sinai School of Medicine, 1 East 100th Street, Box 1135, New York, NY 10029, USA

Mikhail Kunin,

Department of Computer and Information Science, City University of New York (Brooklyn College and Graduate Center), Brooklyn, New York, NY, USA

Theodore Raphan, and

Department of Neurology, Mount Sinai School of Medicine, 1 East 100th Street, Box 1135, New York, NY 10029, USA

Department of Computer and Information Science, City University of New York (Brooklyn College and Graduate Center), Brooklyn, New York, NY, USA

Bernard Cohen

Department of Neurology, Mount Sinai School of Medicine, 1 East 100th Street, Box 1135, New York, NY 10029, USA

Mount Sinai School of Medicine, New York, NY, USA

Mingjia Dai: Mingjia.dai@mssm.edu

Abstract

We tested the hypothesis that motion sickness is produced by an integration of the disparity between eye velocity and the yaw-axis orientation vector of velocity storage. Disparity was defined as the magnitude of the cross product between these two vectors. OVAR, which is known to produce motion sickness, generates horizontal eye velocity with a bias level related to velocity storage, as well as cyclic modulations due to re-orientation of the head re gravity. On average, the orientation vector is close to the spatial vertical. Thus, disparity can be related to the bias and tilt angle. Motion sickness sensitivity was defined as a ratio of maximum motion sickness score to the number of revolutions, allowing disparity and motion sickness sensitivity to be correlated. Nine subjects were rotated around axes tilted 10°–30° from the spatial vertical at 30°/s–120°/s. Motion sickness sensitivity increased monotonically with increases in the disparity due to changes in rotational velocity and tilt angle. Maximal motion sickness sensitivity and bias (6.8°/s) occurred when rotating at 60°/s about an axis tilted 30°. Modulations in eye velocity during OVAR were unrelated to motion sickness sensitivity. The data were predicted by a model incorporating an estimate of head velocity from otolith activation, which activated velocity storage, followed by an orientation disparity comparator that activated a motion sickness integrator. These results suggest that the sensory-motor conflict that produces motion sickness involves coding of the spatial vertical by the otolith organs and body tilt receptors and processing of eye velocity through velocity storage.

Keywords

Vestibular; Angular vestibulo-ocular reflex (aVOR); Off-vertical axis rotation (OVAR); Nystagmus; Velocity storage; Motion sickness; Human

Introduction

Motion sickness, which has affected travelers for centuries, is comprised of symptoms that include malaise, sweating, pallor, dizziness, disorientation, drowsiness, nausea and emesis (Darwin 1796; Irwin 1881; Kucharczyk et al. 1991; Yates 1992; Yates and Miller 1998; Balaban 1999). Some or all of these symptoms occur in association with angular movement of the subject or the visual surround around axes tilted from the spatial vertical (Guedry and Benson 1978; Cheung et al. 1991), with linear oscillation (Golding and Kerguelen 1992) and with circular or zooming movement of the visual surround (Hettinger et al. 1990). Symptoms of motion sickness are also present on entry and return from space. This space sickness has been postulated to be due to adaptation of the vestibular system to micro-gravity and to the re-adaption upon re-entry to a gravitational environment (Graybiel et al. 1975; Money 1981; Matsnev et al. 1983; Igarashi and Kobayashi 1985; Thornton and Uri 1991; Putcha et al. 1999). One of the prevailing hypotheses to explain the development of motion sickness is the sensory conflict theory (Reason and Brand 1975), which was modeled by Oman (Oman 1982). The conceptual basis of the model is that when motion stimuli activate sensory neural information from different modalities that conflict with that generated by an internal model, motion sickness is generated. While there is general agreement with this idea, the exact nature of the conflict and the neural mismatch that induces motion sickness are not known. One purpose of this study was to develop an explicit model of the nature of this conflict.

Bles and colleagues showed that subjects developed motion sickness if they were rotated about a horizontal axis, but not if they were rotated around a vertical axis (Bles 1988; Bos et al. 2002). They postulated that the conflict was related to deviation of the sensed vertical, integrated from all sensory systems, from the subjective vertical (Bles 1988). This conflict formed the basis of their predictive model of motion sickness for vertical linear acceleration (Bos and Bles 1998). Using a paradigm of rolling the head while rotating at a constant velocity, originally developed in the NASA Space Program (Graybiel and Wood 1969; Guedry and Benson 1978; Lackner and Graybiel 1986), we found a relationship between motion sickness sensitivity and deviation of the axis of eye rotation from the yaw axis orientation vector of velocity storage in the vestibular system (Dai et al. 2003). In these experiments, the head was rolled laterally 45° from the upright while subjects rotated at a constant velocity about a spatial vertical axis in darkness. This caused activation of the vertical canals, as they came into the plane of rotation, and induced vertical nystagmus that deviated the axis of eye velocity from the spatial vertical. Concurrently, it produced a sense of pitching forward or back, associated with a surge of motion sickness that subsided to a stable level that steadily increased with each subsequent roll head movement (Dai et al. 2003).

An important outcome of this work was that motion sickness sensitivity decreased as the velocity storage component of the vestibular response decreased (Dai et al. 2003, 2007). From these data, we proposed that motion sickness was generated through velocity storage and that the sensory conflict was related to a disparity between the eye velocity vector generated in velocity storage in the vestibular system and its yaw axis orientation vector, which in upright or tilted positions on average is close to gravity. We further postulated that the disparity was integrated by a motion sickness integrator (Benson 1984) in the autonomic

system that was responsible for the buildup in motion sickness over the time that the disparity was present. Therefore, motion sickness was dependent not only on the time constant of the autonomic motion sickness integrator, but also on the time constant of velocity storage. Because the response to each head movement included a surge as well as an increment in the steady state level of motion sickness, the quantitative relationship between motion sickness sensitivity and disparity could not easily be obtained from these transient motions.

A better approach for assessing the relationship between motion sickness and disparity would be to utilize yaw rotation in darkness about an axis that was tilted from the vertical, i.e., off-vertical axis rotation (OVAR). Eye velocity elicited by yaw axis OVAR is composed of a steady-state horizontal slow phase velocity (bias) level and of oscillations in horizontal, vertical, and roll eye position and velocity (Guedry 1965; Benson and Bodin 1966; Young and Henn 1975; Dai et al. 1994; Dai et al. 1996; Haslwanter et al. 2000; Kushiro et al. 2002). OVAR also induces vergence and divergence related to backward and forward head positions, respectively (Dai et al. 1994) and is well known to produce motion sickness (Guedry 1965; Benson and Bodin 1966). The bias velocity is produced by activation of velocity storage by a velocity estimate obtained from the sequential activation of polarization vectors associated with otolith afferents as the head rotates in the gravitational field (Raphan and Schnabolk 1988; Fanelli et al. 1990; Schnabolk and Raphan 1992). The tilt angle and rotational velocity can be varied independently to obtain different values of the bias velocity. The magnitude of the disparity can then be controlled and computed from the bias velocity and tilt angle. Furthermore, motion sickness elicited by OVAR develops smoothly, allowing for precise determination of how the disparity between the yaw axis orientation vector and the eye velocity vector is related to the generation of motion sickness. We also intended to determine the optimal combination of OVAR tilt angles and rotation velocities that produce the maximum bias velocity during OVAR and whether this maximal bias velocity was associated with the induction of maximal motion sickness.

Methods

Subjects

Nine subjects (5 women, 4 men, ages 21–32) participated in the study. The gains and time constants of their angular vestibulo-ocular reflex (aVOR) were within normal limits (Dai et al. 1999). None had a history of vestibular disease or susceptibility to motion sickness, i.e., car sickness, air sickness or sea sickness. They had not been tested before with OVAR or with cross-coupled stimuli for motion sickness susceptibility. The procedures were explained in detail to them including the likelihood of having symptoms of motion sickness, such as disorientation, dizziness, sweating, and nausea. After agreeing to participate, subjects signed an informed consent form that was approved by the Institutional Review Board of the Mount Sinai School of Medicine, New York.

Test protocol

Subjects sat in a motor-driven rotating chair that was enclosed in a light-tight, circular room, two meters in diameter. The Z-axis of the head and body was aligned with the axis of yaw rotation, which produced $\approx 25\text{--}30^\circ$ of upward tilt of Reid's line. Horizontal and vertical positions of the right eye were recorded by video-oculography (ISCAN) at 60 fr/s with an accuracy of $>0.5^\circ$ over $\pm 30^\circ$. Eye position was calibrated while subjects watched a laser dot displayed in front at angles of $\pm 15^\circ$ horizontally and 15° upward. Eye positions and slow phase eye velocities were positive for movements to the left and down from the subject's perspective. All subsequent testing was done in darkness.

Each subject received two different sets of three stimuli: (1) Constant velocity rotation at $60^\circ/\text{s}$ with tilts of the axis of rotation of 10° , 20° , and 30° . This tested for effects of changes in the axis of rotation from the spatial vertical on eye velocity and motion sickness. (2) Constant velocity rotation at $30^\circ/\text{s}$, $90^\circ/\text{s}$ or $120^\circ/\text{s}$ at 30° tilt of the axis of rotation. This tested for effects of the velocity of rotation on eye velocity and motion sickness. Each subject was tested once a week. One of the six test conditions was randomly assigned to each subject to reduce possible contamination by the psychological effects in the first OVAR experience. Baseline aVOR gains and time constants were determined from steps of constant velocity rotation ($60^\circ/\text{s}$, $200^\circ/\text{s}^2$) from two per-rotatory and two post-rotatory steps of velocity before each OVAR test.

During OVAR, the subject's body was securely fastened to the chair with a 3-point seat belt, a chest pad support, and thigh and leg holders. The subjects wore a helmet that held the camera that sensed eye position. The helmet was firmly held to the back of the chair by a V-block head rest. The neck was supported with a soft pillow placed behind the neck. Two positional sensors (Seiko, resolution 0.01° , maximal measured angle $\pm 80^\circ$), one on the V-block and the other on the helmet, were used to record head position with respect to gravity as well as to monitor any position change between the support block and head during and after OVAR. The phase of two sensors did not change. This indicated that the head had not moved relative to the head rest. The subject, rotating chair, and OVAR room were continuously monitored by an infra-red surveillance camera. Eye positions were also shown on a monitor to determine the alertness of the subject and to follow any changes in eye position due to slip of the helmet on the head. At the beginning and end of the test, the image of the pupil of the right eye was confined to a small rectangular area when the eye was fixating a laser dot in front of the subject. This indicated that the camera had not moved relative to the eye. There was little eye position change before and after OVAR and no head position change.

The OVAR test procedure and recordings are shown in Fig. 1. Each OVAR test session began with the subject seated upright in darkness. The chair was rotated to the right about a spatial vertical (yaw) axis to a predetermined velocity of $30\text{--}120^\circ/\text{s}$ with an acceleration of $200^\circ/\text{s}^2$. When the per-rotatory nystagmus had decayed to zero after 60 s, a spot of light was displayed for 10 s that was stationary with respect to the subject to dump any residual nystagmus. Two seconds after the light went out, the rotating chair and the enclosure were tilted together to a predetermined angle of 10° , 20° or 30° from the spatial vertical using an electric-hydraulic system (Neurokinetics). Tilt durations were 15 s, regardless of the tilt angle. These slow tilts, which were maximally $2^\circ/\text{s}$ for a tilt angle of 30° , would only minimally activate the canals. The ambient temperature in the OVAR enclosure was regulated and maintained at $18\text{--}20^\circ\text{C}$, using an air conditioner. Electrodermal responses, EDR, were taken to correlate with the subjective reports of motion sickness. Two standard Ag/AgCl ECG electrodes placed on the forehead 5 cm apart were used for the measurement of phasic changes in skin conductance due to perspiration.

Analysis of data

Horizontal and vertical eye positions from the ISCAN system were filtered with analog filters from DC to 20 Hz before being resampled by a PC at 600 Hz/channel. Eye position data were digitally differentiated to obtain slow phase eye velocity. Quick phases were removed, leaving slow phase eye velocity for analysis (Fig. 1a, gray line). The gain of the horizontal aVOR was obtained from the ratio of the initial slow phase eye velocity/head (chair) velocity. The dominant time constant of the aVOR was obtained from fits of slow phase eye velocity by the velocity storage model (Dai et al. 1999) and averaged from the two per- and two post-rotatory tests. Group means of the aVOR time constants and step gains in the nine subjects in each test sequence are shown in Table 1. Modulations and bias

velocities of horizontal eye velocity during OVAR were taken from sine fits of 15 cycles, 10–20 s after the chair had reached a final tilt position, as shown in Fig. 1a (black line). One-way repeated measures ANOVA and linear least squares regressions were used for the data analyses unless specified.

Estimation of disparity

Disparity was defined as the magnitude of the cross product between the horizontal bias velocity during OVAR and a unit vector along the direction of the acceleration of gravity (Dai et al. 2006a) given by:

$$D_o = \|\vec{\omega}_{yvs} \wedge \hat{a}_{yo}\| \quad (1)$$

where D_o is the disparity, $\vec{\omega}_{yvs}$ is the yaw (horizontal) angular velocity storage component (bias), $\hat{a}_{yo}$ is the unit vector along the yaw orientation vector, which is taken to be aligned with the spatial vertical. The operators $\wedge$ and $\|\cdot\|$ represent the cross product and norm (magnitude), respectively.

In monkey, the yaw axis orientation vector of velocity storage tends to align with the spatial vertical for static tilts up to 40–50° when horizontal eye velocity moves the eyes toward gravity, but the alignment is shifted toward the body vertical when horizontal eye velocity moves the eyes away from gravity (Dai et al. 1991; Raphan et al. 1992). There are also alignments of the yaw orientation vector with the spatial vertical during supine and prone positions (Raphan et al. 1992). Because the head is continually rotating and changing orientation during OVAR, the orientation vector oscillates. When the tilt is less than 30° (Dai et al. 1991), as in this study, there is a Mueller effect, which overestimates the direction of the orientation when side down. Therefore, we expect that, on average, the yaw orientation vector is close to the spatial vertical over each cycle of OVAR. A similar conclusion was reached in an analysis of the time constant changes and average orientation changes in eye velocity in the monkey during OVAR (Kushiro et al. 2002). Studies of the orientation properties of OKN in humans (Gizzi et al. 1994) also suggest that the yaw axis orientation vector is close to the spatial vertical.

Based on the assumption that the average yaw orientation vector is close to the spatial vertical while the average eye velocity vector is along the head vertical during OVAR, the disparity, D_o , is equal to the product of the magnitude of horizontal eye velocity (bias) and the sine of the angle of tilt.

$$D_o = \|\vec{\omega}_{yvs}\| \sin \theta \quad (2)$$

Because of the assumption that the orientation vector utilized is a normalized unit vector, it has no units. As a result, the units for disparity are angular velocity; given as rad/s or °/s. If hypergravity or hypogravity affects the magnitude of the yaw axis orientation vector, then the definition given in Eq. (2) could be extended:

$$D_o = \|\vec{\omega}_{yvs}\| f \sin \theta \quad (3)$$

where f is a unitless factor, which is greater than 1 for hypergravity and less than 1 for hypogravity. Regardless, the units associated with disparity would remain as °/s.

For a given angle of tilt, θ , the disparity should be linearly related to bias velocity. Similarly, for angles of tilt (θ) up to 30° the sine of the angle as a function of tilt angle is approximately linear. Therefore, using Eq. (2), any disparity in this range should have an approximate linear relationship with tilt angle for a given rotational velocity.

Motion sickness sensitivity

Before the first OVAR test, subjects were trained to report their motion sickness score with a simplified Pensacola scale from 0 to 20 (Hecht et al. 2001; Young et al. 2001). Zero was no reaction; 5 was starting to feel warm; 10 was moderate gastro-intestinal distress and/or dizziness, plus sweating; 15 was a strong feeling of nausea or dizziness, but subjects could still carry on with the test; and 20 was the end point at which time, subjects felt they could go no further. This could be due to a sense of imminent emesis or a strong sense of dizziness, which could have come from hypocapnea or a drop in blood pressure (Cohen et al. 2010). Subjects were in continuous communication with the experimenters during the test. The score of motion sickness was reported verbally every 15–60 s, depending on the pace of development of motion sickness. The test was stopped automatically after 15 min from the start of OVAR if the motion sickness end point had not been reached. Thus, for example, for rotation at $60^\circ/\text{s}$, the subject would have had a maximum of 150 rotations. For inter-individual comparisons, an index of motion sickness sensitivity was used, which was a ratio between the final score and number of revolutions that subjects had completed. Because there was intersubject variability in the final score they could achieve, this normalized metric, which has units of score per head turn allowed for a more consistent comparison between subjects. Therefore, the motion sickness sensitivity was larger for more susceptible subjects and vice versa.

Results

General

All nine subjects completed the six OVAR test sessions. The time constants (TC) and gains of the horizontal aVOR, tested at the beginning of each session, were not statistically different over the six tests (TC: $P=0.09$, $F=2.07$, $df=5$, ANOVA; gains: $P=0.87$, $F=0.36$, $df=5$; Table 1). Therefore, we could conclude that the baseline testing and the OVAR tests that were performed once a week had not significantly habituated the aVOR time constants or changed the step gains of the aVOR. In a typical OVAR experiment, the chair was upright at the onset of the test. Rotation to the right at $60^\circ/\text{s}$ in darkness induced horizontal per-rotatory slow phase velocity that reached $46^\circ/\text{s}$, and then declined to zero in 50 s (Fig. 1a). There was little or no vertical eye velocity. Torsional eye movements, which characteristically oscillate from side to side during yaw axis OVAR, were not recorded in this study. At the 72th s, the chair inclined to 30° in 15 s while still rotating. The eye oscillated, climbing to a bias level of $6.52^\circ/\text{s}$ (Fig. 1a, horizontal dashed line). The steady state bias level was reached about 36 s from the onset of the OVAR tilt. The oscillations in eye velocity as a function of head position relative to gravity were well approximated with a sine function (Fig. 1a, black solid sinusoidal line).

The baseline skin conductance at rest was 11.3 microseimens in this subject (Fig. 1c). Skin conductance did not change over the initial eight cycles of OVAR rotation, but rose quickly to a relatively stable level of 28 microseimens over the next 25 s, associated with a sudden rise in sweating (Fig. 1c, abrupt sweating period). Six of nine subjects had similar changes in patterns of skin conductance over the forehead. The other three reported perspiration at the axillae, and there was little or no conductance change on the forehead. The baseline skin conductance for the six subjects who sweated on the forehead was 9.2 ± 6.6 microseimens, which rose to a stable level of 21.5 ± 9.4 microseimens when tested with yaw

axis OVAR rotation at 60°/s and 30° tilt. After reaching a “plateau”, there was a further small rise and fluctuation in skin conductance in some individuals (Fig. 1c). The time from the onset of OVAR to the onset of the rapid rise in sweating varied considerably around 240 ± 128 s. Thus, changes in skin conductance at the forehead were not uniformly present in all subjects, but when present, could be used as an objective indication of motion sickness.

Effects of OVAR tilt angles and rotation velocities on bias velocity

To test effects of tilt angle on slow phase eye velocity, the rotation velocity was fixed at 60°/s and subjects were rotated around axes of rotation tilted 10°, 20° and 30° from the spatial vertical. The average horizontal bias velocity of the nine subjects increased monotonically along with increases in the angle of the tilt, from 1°/s at 10° tilt to 6.5°/s at 30° tilt (Fig. 2a). The largest bias velocity was 6.5°/s at 30° tilt, and the changes in bias velocity as a function of tilt angle were significant ($P < 0.0001$, $df = 2$, $F = 42$). To test effects of rotational velocity on eye velocity, the tilt angle was fixed at 30° and rotation velocities were varied from 30 to 120°/s with an interval of 30°/s. The bias velocity declined significantly for lower and higher rotational velocities than 60°/s (Fig. 2b).

Motion sickness as a function of time and the disparity

The development of motion sickness over time was examined in nine subjects for an OVAR rotational stimulus of 60°/s and tilt of the axis of rotation of 30° (Fig. 3). On average, the motion sickness score at the time when the axis of rotation reached 30° tilt angle was 0.9 ± 1.0 , indicating that although the value of the score was small, motion sickness had developed in some subjects during the period of the tilt. When the chair and enclosure were fully tilted, the rise in motion sickness over time was relatively smooth, but the rate of rise varied considerably among subjects (Fig. 3). Only one subject could complete 15 min of OVAR. The slow but steady buildup of motion sickness over time in each of our subjects is consistent with the previous hypothesis of Benson that motion sickness is likely to evolve through a process of integration (Benson 1984, 2002).

The magnitude of the disparity over the six tests was calculated for each subject and related to their motion sickness sensitivity (Fig. 4). In each individual, there was a positive linear relationship between motion sickness sensitivity over the six tests and the increase in the disparity. However, there were large differences in the slopes of the linear fits. Subjects **b–h** had similar slopes, ranging from 0.04 to 0.08. Subject **a** had the steepest slope, 0.16, indicating that he was the most sensitive to the changes in disparity, whereas subject **i** had a flat slope, 0.006, indicating that he was most refractory. Thus, while motion sickness sensitivity increased linearly with increases in the disparity in each subject, the differences in slopes probably reflected differences in sensitivity of the autonomic system to the changes in the disparity.

Motion sickness sensitivity (MSS) and bias velocity were plotted against the velocity of rotation around an axis tilted by 30° (Fig. 5). Both motion sickness sensitivity and bias velocity peaked at a velocity of rotation 60°/s and were significantly less at lower and higher rotation velocities ($P \leq 0.01$; two-tailed, paired *t*-tests). Since the maximum bias velocity reflected the maximal activation of velocity storage, the coincidence of the maximal bias velocity and the maximal motion sickness sensitivity provides strong support for the contention that motion sickness was produced through velocity storage.

Modulation in slow phase eye velocity during OVAR

We next determined whether there was a similar relationship between peak-to-peak modulations in eye velocity and motion sickness sensitivity. Peak-to-peak modulation in eye velocity increased significantly with increases in rotational velocity ($P < 0.0001$, $df = 3$, F

=11.6), changing from 7.5°/s at 30°/s to 17°/s at 120°/s (Fig. 6a). The amplitude of the modulations in eye velocity also rose significantly ($P < 0.0001$, $df = 2$, $F = 62.6$) as the stimulus was changed from 5°/s at 10° tilt of the axis of rotation to 12.5°/s at 30° tilt (Fig. 6b). Thus, in contrast to bias velocity (Fig. 2a), modulations in eye velocity increased with increases in both rotational velocity and angle of tilt of the axis of rotation over the full range of stimuli that were used. These findings are in good agreement with those of others who also showed that the amplitude of modulation in eye velocity increased with the increases in rotational velocity (Darlot et al. 1988; Wood 2002) and with increases in the tilt angle (Darlot et al. 1988; Haslwanter et al. 2000).

In contrast to the linear relationship between the amount of disparity and motion sickness sensitivity shown in Fig. 4, however, there was no relationship between the modulation in eye velocity and individual motion sickness sensitivity (Fig. 7).

Conceptual framework for generation of motion sickness induced by OVAR

A model of motion sickness incorporated these findings (Fig. 8) and simulations allowed us to test the model's prediction (Fig. 9). In the model, the motion sickness state is the output of a motion sickness integrator, which is part of the autonomic system. The motion sickness state is essentially a "pattern vector" whose components are the autonomic features, such as nausea, sweating, dizziness, etc. One of these features (sweating, Fig. 1b) was directly measured by skin conductance. It had a rising characteristic, consistent with that produced by an integrator with a time constant of about 25–30 s. The time constants for the integrators for other features of motion sickness could be minutes, hours or days. The symptoms of motion sickness produced either by neural activity or through hormonal changes have not been measured objectively. Such measurements are beyond the scope of this study.

The motion sickness integrator is driven by the output of an orientation comparator, which is the magnitude of the cross product of the yaw-axis orientation vector of velocity storage and the eye velocity vector generated by velocity storage. The orienting comparator activates a parametric controller in the nodulus/uvula (Wearne et al. 1998), which determines the yaw-axis orientation vector. This vector determines the cross-coupled eye velocity that shifts the yaw axis orientation of velocity storage toward alignment with the gravitational vertical and also modifies the time constants of velocity storage (Sturm and Raphan 1988; Raphan and Sturm 1991). We have assumed that this yaw axis orientation vector remains aligned with the spatial vertical. Because of the dynamics and changes in cross-coupling parameters (Dai et al. 1991), eye velocity generated through velocity storage will not necessarily be aligned with the yaw orientation vector. The disparity between the orientation vector and eye velocity activates the autonomic system to generate the buildup of motion sickness through the motion sickness integrator for as long as the error is maintained.

The velocity storage integrator is activated by an otolith velocity estimator, which matches (correlates) a rotating pattern of activation of otolith polarization vectors with a neurally delayed pattern as the head rotates during OVAR (Raphan and Schnabolk 1988; Schnabolk and Raphan 1992). The delay determines an upper bound on the velocity generated during OVAR (Raphan and Schnabolk 1988) and the neural network structure predicted the independence of velocity generation on tilt angle past a threshold in monkeys (Raphan and Schnabolk 1988; Fanelli et al. 1990; Koshiro et al. 2002). The similarity of the human data to those of the monkey verifies the predictions of Raphan and Schnabolk (Raphan and Schnabolk 1988) and Fanelli and Raphan (Fanelli et al. 1990) that there is a limitation of recognition of angular velocity by the otolith organs, which justifies the use of the estimation in the present model of OVAR in humans.

The model was implemented as a Matlab and C/C++ program using the building blocks shown in Fig. 8. The otolith velocity estimator was implemented using a pattern matching algorithm, which compared the rotating pattern of sinusoidal otolith activation with a neurally delayed pattern of otolith activation (Raphan and Schnabolk 1988; Schnabolk and Raphan 1992). Velocity storage was implemented as a three-dimensional integrator whose system matrix has eigenvalues and cross-coupled matrix terms that varied as a function of head orientation with regard to gravity (Raphan and Sturm 1991; Kushiro et al. 2002).

Model simulations

Simulations of the yaw eye velocity and motion sickness were consistent with the data for OVAR at different rotational velocities at a fixed tilt angle (Fig. 9a–d) as well as for different tilt angles at the same rotational velocity (Fig. 9e–h). The model predicted that the estimation of head velocity during OVAR would increase with head velocity, having a peak value at 60°/s, but would then decline as the sinusoidal patterns emanating from the otolith organs had reductions in correlation at higher velocities of rotation. A delay of 0.85 s was shown to fit OVAR data of the monkey (Raphan and Schnabolk 1988) and is consistent with a delay of 1 s in the buildup of eye velocity following the tilt at the start of OVAR (Fanelli et al. 1990).

The model also predicts that there would be an increase in the bias velocity as a function of tilt up to about 30° and that this would normalize, i.e., remain fixed, for greater angles and a fixed velocity (Fig. 9e, f). This is evident in the data of the monkey (Fanelli et al. 1990; Kushiro et al. 2002). Our data in humans show that the bias velocity peaks at 60°/s and then declines (Fig. 2b). This implies that a normalization occurs over a lower velocity range (0–60°/s). It could also possibly occur for tilts larger than 30°, but these were beyond the capabilities of our equipment. Despite parametric differences in bias velocity generation during OVAR between monkeys and humans, motion sickness sensitivity was related to the disparity in the generation of eye velocity through velocity storage, and the model predicted these findings (Fig. 9c, d, g, h). The motion sickness state rose in conjunction with the disparity at a fixed angle of tilt with varying velocities of rotation (Fig. 9c, d) as well with a fixed velocity of rotation and varying tilts (Fig. 9g, h).

The autonomic reactions associated with motion sickness that we have modeled by an integration process (Fig. 8) may also hold true for other autonomic features in addition to the malaise monitored by MSS score. An example is perspiration measured by skin conductance. It lagged the onset of motion sickness and had a shorter rising time course (Fig. 1b). Nevertheless, this is in accord with the implementation of a motion sickness integrator within the autonomic system, which is driven by the orientation disparity (Fig. 9d, h).

Discussion

The major finding of this study is that motion sickness induced by OVAR is closely related to the magnitude of the disparity between the bias velocity produced by velocity storage in the vestibular system and the yaw axis orientation vector, which is close to gravity. Thus, it is a function of the magnitude of each vector and the sine of the angle between them. This finding extends the results of our study on roll while rotating (Dai et al. 2003, 2007), in which we proposed that a disparity in the velocity storage network triggered the autonomic system to produce the symptoms of motion sickness. OVAR provided a better experimental tool for determining this, since subjects rotated at a chosen velocity about an axis that was tilted at a known angle with regard to gravity, and the angle of tilt and the velocity of rotation could be varied independently. Moreover, the disparity was maintained continuously at a constant level throughout the exposure to OVAR. As a result, motion

sickness developed smoothly and progressively (Fig. 3), and the steady buildup could be simulated as an integration process driven by the orientation disparity (Figs. 8, 9). We postulate that processing for this integration occurs in the nodulus and uvula of the vestibulo-cerebellum (Cohen et al. 2003), since spatial orientation of velocity storage disappears after removal of the nodulus and uvula (Wearne et al. 1996) and bias velocity in response to OVAR is abolished (Angelaki and Hess 1995). Motion sickness sensitivity is also dramatically reduced or lost after nodulus and uvula lesions (Bard 1945; Wang and Chinn 1956).

By changing the rotational velocity and the angle between gravity and the rotational axis, we were able to establish that the maximum disparity was produced by rotation at $60^\circ/\text{s}$ around an axis tilted 30° (Fig. 2a). This rotational velocity had the largest effect in producing motion sickness (Fig. 5), supporting our hypothesis. Since the disparity is a function of the amplitude of the vectors in velocity storage, a reduction in bias velocity would reduce the disparity, and these velocities would produce less motion sickness.

Although we assumed the orientation vector to be aligned with gravity, we did not simply use gravity as the reference for disparity because of a conceptual constraint in how the otoliths sense acceleration. When the head is in continual motion, the otoliths sense the composite linear acceleration, and gravity is just an equivalent acceleration component. So, during OVAR, it would be difficult to justify that the central nervous system always maintains an exact representation of the direction of gravity for every head position. Rather, our hypothesis that the *average* yaw orientation vector is close to the spatial vertical seems better justified. We further maintain that it is more justifiable to consider that the central nervous system codes an estimate of the direction of the prevailing GIA, which varies with time. Since motion sickness is intimately tied to velocity storage (Dai et al. 2003), a reasonably good estimate of the reference for computing disparity is the average yaw orientation vector, which is maintained close to the spatial vertical.

In a comprehensive study, Haslwanter et al. (2000) used tilt angles from 15° – 90° and a rotational velocity of $100^\circ/\text{s}$ and had maximum bias velocities at 60° tilt. The maximum bias velocities in five subjects on average were $4^\circ/\text{s}$, which was somewhat smaller than the $6.5^\circ/\text{s}$ obtained in this study. The induction of OVAR was different in the two studies. The axis of rotation was tilted only after the aVOR response had completely disappeared in our study, whereas, OVAR and the aVOR were activated together in the tilted position in Haslwanter et al.'s study. The latter is a more complex stimulus, since a step of velocity at the onset of rotation due to the excitation of the cupula/endolymph system is followed by a decline in slow phase velocity, while at the same time, the velocity builds due to otolith activation by rotation about a tilted axis. There also can be secondary after-nystagmus after the step of velocity. Interaction between these factors may account for the lower value of the bias in their study.

Raphan and colleagues (Raphan and Schnabolk 1988; Fanelli et al. 1990; Schnabolk and Raphan 1992) modeled OVAR and concluded that limits in bias velocity during rotation about tilted axes would come from limits in estimating head velocity from the pattern and delayed pattern generated by the otolith organs as the gravity vector swept across the utricles and saccules (See "Appendix"). Thus, a general limitation of processing otolith information when estimating head and body velocity in space could be a fundamental constraint in determining disparity and motion sickness sensitivity during OVAR, regardless of rotational speed or angle of tilt of the axis of rotation. Another limitation could be the saturation of the velocity command within velocity storage. Regardless of limitations for phase detection, however, it is worth emphasizing that angular head velocity can be determined centrally from otolith activation when the head rotates in any plane other than the horizontal (Young

and Henn 1975; Schnabolk and Raphan 1992; Angelaki and Hess 1996). Similarly, a sense of angular rotation of the body can also come from the somatosensory system through velocity storage (Bles et al. 1983; Bles and Kotaka 1986; Solomon and Cohen 1992a, b; Sugita-Kitajima and Koizuka 2009) and possibly from body tilt receptors (Yates et al. 2000).

Our finding that peak motion sickness occurred at 60°/s of rotational velocity is in agreement with findings of McCauley et al. (1976) who employed vertical linear acceleration to elicit motion sickness. In an extensive study, they found that the most provocative linear stimulation occurred at oscillation at 0.17 Hz. This corresponds to a frequency of rotational velocity during OVAR of 60°/s, which was where we also found the maximum response. Interestingly, Golding et al. (Golding et al. 2009) found that oscillation of the visual surround at 0.2 Hz about a yaw axis while the head was tilted (visual OVAR) is nauseogenic. Donohew and Griffin (Donohew and Griffin 2009) also found that 0.2 Hz of lateral oscillation is most provocative. As yet, the central basis for development of motion sickness from oscillating linear acceleration and visual stimulus is not known, but it is striking that both OVAR and linear acceleration involve the otolith organs. Therefore, there is likely to be a common mechanism for production of motion sickness from both stimulus conditions.

Denise et al. (1996) reported that the most provocative stimulus velocity to produce motion sickness was 105°/s. There are a number of differences in the studies that could account for the apparent difference. Denise et al. used 18 subjects in each of six groups for each stimulus run. Each subject was only tested once, and they compared groups, rather than comparing the motion sickness induced by the different OVAR stimulus velocities and different tilts of the axis of rotation in the same individuals. They also used 'moderate motion sickness' to terminate the test, which could vary among individuals who are only tested once. In our study, we used an end point (about to vomit) to terminate the test that could be compared in each subject under the different stimulus conditions, and we randomized the six paradigms to avoid possible contamination from psychological effects of the first OVAR test. With regard to this, it was surprising that in Denise et al.'s study, the mean of moderate motion sickness occurred after 15 min of rotation of 60°/s and 30° tilt. By comparison, most of our subjects could not finish even 15 min of OVAR on the first test before coming to the final endpoint (about to vomit) at a smaller tilt angle.

What could not be done with OVAR, however, was to change the magnitude of the gravito-inertial acceleration (GIA) to enhance or diminish the disparity. This was done, however, during parabolic flight (Lackner and DiZio (2009) and during Spaceflight (Clément et al. 2001). In those conditions, a cross-coupled angular stimulus (moving the head while rotating) became worse when the gravitational force was increased and had less effect when the gravitation force was reduced (Lackner and Garybiel 1986). Moreover, no motion sickness was induced when the head was pitched while rotating in microgravity (the M131 phenomenon, Spacelab Mission; Graybiel et al. 1977). While general postulates have been proposed to explain these phenomena (Lackner and Graybiel 1986; Lackner and Dizio 2009), no specific mechanism has explained them. Based on our model, the yaw axis orientation vector is normalized on Earth to the acceleration of gravity. Hypergravity would increase the gravitational vector, which would alter the magnitude of the weighting of the orientation vector in determining disparity ("Methods", Eq. (3)). Consequently, the disparity between the eye velocity vector of velocity storage and the orientation vector would be increased for a given angle, resulting in an increase in motion sickness sensitivity. The reverse would occur during epochs of hypogravity of parabolic flight and during microgravity in Space, in which the gravitational vector is less than 0.00001 g. Consequently, the disparity is essentially zero in microgravity. Thus, after initial adaptation,

it then would become possible for the astronauts to rotate their head during rotation without becoming nauseated.

The time constant represents a fundamental property of velocity storage, i.e., the leak of the integrator. Therefore, it would be expected that the bias velocity would be smaller if the time constant were reduced and that the disparity would be less effective in inducing motion sickness. Since the dominant time constant of the aVOR, which largely represents the time constant of velocity storage, did not change in this series of experiments (Table 1), it was not possible to test this hypothesis. However, a reduction in motion sickness sensitivity in conjunction with a reduction in time constant of the aVOR, due to habituation, was shown in previous studies on roll while rotating (Dai et al. 2003, 2007). Furthermore, administration of baclofen, a GABA_B agonist, which reduces the velocity storage time constant (Cohen et al. 1987; Dai et al. 2006b), also reduces motion sickness on a dose-by-time constant reduction (Cohen et al. 2008). Moreover, after velocity storage is reduced by pharmacological means or by lesions, velocity storage and motion sickness are significantly reduced or abolished (Gordon et al. 1996; Johnson et al. 1999; Dai et al. 2007). Conversely, a number of studies have shown that the vestibular time constant tends to be longer in susceptible subjects (Shupak et al. 1990; Gordon et al. 1996; Bos et al. 2002; Hoffer et al. 2003), compatible with the idea that motion sickness is related to an orientation disparity and that the time constant of velocity storage affects that disparity.

A conclusive finding of our study was that the modulations in eye velocity during OVAR, produced by the changes in head position relative to gravity, were unrelated to generation of motion sickness. This finding was present individually in 8 of the 9 subjects in our study (Fig. 7). Furthermore, since the amplitude of modulation of eye velocity during OVAR increases monotonically as a function of head position relative to gravity with increases in rotational velocity, but does not saturate (Wood 2002; Ventre-Dominey et al. 2008, present study), while the maximal motion sickness was produced by rotation at 60°/s, not 120°/s. In confirmation, Guedry (1974) produced little or no bias velocity or motion sickness during OVAR about a horizontal axis with a stimulus velocity of 180°/s, although this stimulus produced the maximal modulation in eye velocity. Furthermore, velocity storage and the modulations in eye velocity during OVAR are generated by different neural systems. Velocity storage depends on processing in the rostral MVN and in SVN (Reisine and Raphan 1992; Yokota et al. 1992; Holstein et al. 1999a, b), and is lost after midline section of the brainstem, which interrupts crossing axons of vestibular-only neurons (Blair and Gavin 1981; Katz et al. 1991; Holstein et al. 1999a, b). Specifically, after midline section between the rostral medial vestibular nuclei, the OVAR bias velocity was lost (Holstein et al. 1999b). Horizontal, vertical, and roll orienting eye responses which arise in otolith-ocular neural groups, responsible for the oscillations in eye velocity, on the other hand, are located more caudally in the vestibular nuclei and were unaffected by the midline sections (Katz et al. 1991; Wearne et al. 1997; Holstein et al. 1999a, b).

If the modulations in eye velocity produced by head position re gravity were a critical factor in the production of motion sickness, sinusoidal OVAR, which produces large modulations in eye velocity should be associated with motion sickness. Precisely, the opposite occurs; however, sinusoidal oscillation around a tilted axis produces less not more nausea than OVAR (Furman et al. 1992). Thus, there is a solid body of evidence that indicates that the modulations in eye velocity during OVAR are not a factor in producing motion sickness. This disagrees with conclusions reached by Ventre-Dominey (Ventre-Dominey et al. 2008). The reason for the difference in data is not clear, but these authors never went to the highest levels of motion sickness, and split their subjects into many groups. Therefore, it is hard to be certain that we were comparing similar groups. Regardless, strong evidence supports the

conclusion that motion sickness during OVAR is related to the disparity, not to the modulation in eye velocity as a function of head position relative to gravity.

There are still a number of unanswered questions about the generation of motion sickness. As shown in Figs. 3, there was much individual variation in the development of motion sickness, as well as in the specific aspects of motion sickness, which caused termination of the OVAR. Eight of the nine subjects terminated because they were intensely nauseated, and one because of 'dizziness'. The latter could have been either due to a drop in blood pressure or to hypocapnea due to hyperventillation. Additionally, the slopes of the relationships between motion sickness sensitivity and disparity varied between 0.006 and 0.16, although there was a lawful relationship between motion sickness sensitivity and the disparity in each person (Fig. 4). The reason for the variation is not known, but could reflect differences in autonomic sensitivity to the disparity produced by the vestibular system. Also, unanswered is how motion sickness is induced by pure linear acceleration (O'Hanlon and McCauley 1974; Golding and Benson 1993), by linear visual flow (Cheung et al. 1991), or by looming and zooming. The site of such interactions are unknown, but activity related to these linear or visual motions are likely to be mediated through otolith-related cerebellar pathways where they could interact, based on the disparity in the eye velocity and orientation vectors.

Acknowledgments

DC007847, EY04148, and DC005204. We thank Dmitri Ogorodnikov and Sergey Tarasenko for technical assistance.

Appendix

Estimation of velocity from sequential activation of otolith polarization vectors

In this appendix, we describe the conceptual organization of the velocity estimation as presented in Raphan and Schnabolk (1988) (Fig. 10a), its neural network implementation (Fanelli et al. 1990) (Fig. 10b) and predictions of the estimated Bias Eye Velocity as a function of tilt angle and velocity of rotation (Fanelli et al. 1990) (Fig. 10c). Conceptually, the model implements the estimation of the angular velocity of a rotating wave of otolith afferent activation as the gravity vector sweeps around the head during rotation (Fig. 10a). This is accomplished as a discrete implementation of a ratio of temporal to spatial derivatives. The temporal derivatives are estimated from processing differences between neural activity for a given cell (n) and a central cell that has a delayed version of the activity (Delay (T)). The spatial derivatives are estimated from differences between nearest neighbor polarization vectors.

The neural network implementation of Fig. 10b has a three-layer architecture with 16 neurons to estimate velocity. The estimate is a generalized inner product between temporal and spatial differences. This is a one-sided model, using information from one utricular macula. The difference between the left macula and the right macula estimation is due to mirror symmetry of the numbering of cells. A small leftward rotation of the left macula gives a positive estimate of head velocity, while a small leftward rotation of the right macula gives a negative estimate of head velocity. The K_n 's in the model implement a generalized inner product or bilinear form and account for the fact that the bias component of velocity due to OVAR is approximately independent of tilt angle after it has reached a normalization value.

The weights were adjusted to fit the data on Bias Velocity of head velocities of monkeys, ranging from 0 to 80°/s and tilts of the rotation axis of 0–90° in the model of Fig. 10b. There were 16 units in the input and internal layers. A periodic structure based on pairs of units denoted by A and B was chosen. Connection weights from neighboring units in the input layer converged onto two units in the internal layer. The connection weights were periodically repeated for the eight pairs of units in the internal layer, which because of this symmetry had identical characteristics. Note W_{11} on the solid connection to A_N as well as the shaded one on the right, indicating an example of this symmetry. One such repeating structure is emphasized with the others suggested in gray. There is one output unit. The lowest level represents the equivalent acceleration of gravity on the otolith maculae. The dotted lines indicating pre-processing represent the function transforming the gravitational acceleration into otolith unit activations. The input layer represents the central projections of the otolith units as well as their delayed counterparts.

The key conclusion from this model is that the estimator predicts that the bias eye velocity normalizes at about 30° of tilt (Fig. 10c). For angles of tilt >30°, the estimation increases with rotational velocity and tends to saturate at about 60°/s, where the increments in estimate are no longer proportional to angular velocity. For tilts of the rotation axis less than 30°, the gain of the estimation is small relative to stimulus velocity and a substantial rotational velocity would be necessary to reach significant bias velocities.

References

- Angelaki DE, Hess BJ. Lesion of the nodulus and ventral uvula abolish steady-state off-vertical axis otolith response. *J Neurophysiol.* 1995; 73:1716–1720. [PubMed: 7643178]
- Angelaki DE, Hess BJM. Three-dimensional organization of otolith-ocular reflexes in rhesus monkeys. I. Linear acceleration responses during off-vertical axis rotation. *J Neurophysiol.* 1996; 75:2405–2424. [PubMed: 8793753]
- Balaban CD. Vestibular autonomic regulation (including motion sickness and the mechanism of vomiting). *Curr Opin Neurol.* 1999; 12:29–33. [PubMed: 10097881]
- Bard, P. National Research Council, National Academy of Science. 1945. Subcommittee on motion sickness; Committee on aviation medicine. Report No. 485
- Benson, AJ. Motion sickness. New York: Wiley & Sons; 1984.
- Benson A. Motion sickness. Office of The Surgeon General, Department of the Army, United States of America. 2002
- Benson AJ, Bodin MA. Interaction of linear and angular accelerations on vestibular receptors in man. *Aerospace Medicine.* 1966; 37:144–154. [PubMed: 5295433]
- Blair SM, Gavin M. Brainstem commissure and control of time constant of vestibular nystagmus. *Acta Otolaryngol (Stock).* 1981; 91:1–8.
- Bles W. Coriolis effects and motion sickness modeling. *Brain Res Bull.* 1988; 15:543–549.
- Bles, W.; Kotaka, S. Stepping around: Nystagmus, self-motion perception and Coriolis effects. In: Keller, EL.; Zee, DS., editors. *Adaptive processes in visual and oculomotor systems.* Oxford: Pergamon; 1986. p. 465–471.
- Bles W, Kloten T, Buchele W, Brandt T. Somatosensory nystagmus: physiological and clinical aspects. *Adv Oto-Rhino-Laryngol.* 1983; 30:30–33.
- Bos JE, Bles W. Modelling motion sickness and subjective vertical mismatch detailed for vertical motions. *Brain Res Bull.* 1998; 47:537–542. [PubMed: 10052585]
- Bos JE, Bles W, de Graaf B. Eye movements to yaw, pitch, and roll about vertical and horizontal axes: adaptation and motion sickness. *Aviat Space Environ Med.* 2002; 73:434–436.
- Cheung BS, Howard IP, Money KE. Visually-induced sickness in normal and bilaterally labyrinthine-defective subjects. *Aviat Space Environ Med.* 1991; 62:527–531. [PubMed: 1859339]

- Clément G, Deguine O, Parant M, Costes-Salon MC, Vasseur-Clausen P, Pavy-LeTraon A. Effects of cosmonaut vestibular training on vestibular function prior to spaceflight. *Eur J Appl Physiol.* 2001; 85:539–545. [PubMed: 11718282]
- Cohen B, Helwig D, Raphan T. Baclofen and velocity storage: a model of the effects of the drug on the vestibulo-ocular reflex in the rhesus monkey. *J Physiol.* 1987; 393:703–725. [PubMed: 3446808]
- Cohen B, Dai M, Raphan T. The critical role of velocity storage in production of motion sickness. *Ann N Y Acad Sci.* 2003; 1004:359–376. [PubMed: 14662476]
- Cohen B, Dai M, Yakushin SB, Raphan T. Baclofen, motion sickness susceptibility and the neural basis for velocity storage. *Prog Brain Res.* 2008; 171:543–553. [PubMed: 18718351]
- Cohen B, Yakushin SB, Martinelli GP, Ogorodnikov D, Flores R, Dai M, Holstein GR. Blood pressure and heart rate changes from Labyrinthine stimulation in the anesthetized rat. *Assoc Res Otolaryngol Abs.* 2010; 133
- Dai M, Raphan T, Cohen B. Spatial orientation of the vestibular system: dependence of optokinetic after nystagmus on gravity. *J Neurophysiol.* 1991; 66:1422–1438. [PubMed: 1761991]
- Dai M, McGarvie L, Kozlovskaya IB, Raphan T, Cohen B. Effects of spaceflight on ocular counterrolling and spatial orientation of the vestibular system. *Exp Brain Res.* 1994; 102:45–56. [PubMed: 7895798]
- Dai M, Raphan T, Kozlovskaya I, Cohen B. Modulation of vergence by off-vertical yaw axis rotation in the monkey: normal characteristics and effects of space flight. *Exp Brain Res.* 1996; 111(21–29):21–29. [PubMed: 8891632]
- Dai M, Klein A, Cohen B, Raphan T. Model-based study of the human cupular time constant. *J Vest Res.* 1999; 9:293–301.
- Dai M, Kunin M, Raphan T, Cohen B. The relation of motion sickness to the spatial-temporal properties of velocity storage. *Exp Brain Res.* 2003; 151:173–189. [PubMed: 12783152]
- Dai, M.; Cohen, B.; Kaufmann, H.; Raphan, T. Neuroscience Meeting. Atlanta, GA, USA: Neuroscience Meeting Planner, Georgia World Congress Center, Halls B3–B5; 2006a. Modeling how velocity storage induces motion sickness.
- Dai M, Raphan T, Cohen B. Effects of baclofen on the angular vestibulo-ocular reflex. *Exp Brain Res.* 2006b; 171:262–271. [PubMed: 16341527]
- Dai M, Raphan T, Cohen B. Labyrinthine lesions and motion sickness susceptibility. *Exp Brain Res.* 2007; 178:477–487. [PubMed: 17256169]
- Darlot C, Denise P, Droulez J, Cohen B, Berthoz A. Eye movement induced by off-vertical axis rotation (OVAR) at small angles of tilt. *Exp Brain Res.* 1988; 73:91–105. [PubMed: 3208865]
- Darwin, E. *Zoonomia*. London: J. Johnson; 1796.
- Denise P, Etard O, Zupan L, Darlot C. Motion sickness during off-vertical axis rotation: prediction by a model of sensory interactions and correlation with other forms of motion sickness. *Neurosci Lett.* 1996; 203:183–186. [PubMed: 8742023]
- Donohew BE, Griffin MJ. Motion sickness with fully roll-compensated lateral oscillation: effect of oscillation frequency. *Aviat Space Environ Med.* 2009; 80:94–101. [PubMed: 19198194]
- Fanelli R, Raphan T, Schnabolk C. Neural network modelling of eye compensation during off-vertical axis rotation. *Neural Netw.* 1990; 3:265–276.
- Furman JM, Schor RH, Schumann T. Off-vertical axis rotation: a test of the otolith-ocular reflex. *Ann Otol Rhinol Laryngol.* 1992; 101:643–650. [PubMed: 1497268]
- Gizzi M, Raphan T, Rudolph S, Cohen B. Orientation of human optokinetic nystagmus to gravity: a model based approach. *Exp Brain Res.* 1994; 99:347–360. [PubMed: 7925815]
- Golding JF, Benson AJ. Perceptual scaling of whole-body low frequency linear oscillatory motion. *Aviat Space Environ Med.* 1993; 64:636–640. [PubMed: 8357318]
- Golding JF, Kerguelen M. A comparison of the nauseogenic potential of low-frequency vertical versus horizontal linear oscillation. *Aviat Space Environ Med.* 1992; 63:491–497. [PubMed: 1520219]
- Golding JF, Arun S, Wortley E, Wotton-Hamrioui K, Cousins S, Gresty MA. Off-vertical axis rotation of the visual field and nauseogenicity. *Aviat Space Environ Med.* 2009; 80:516–521. [PubMed: 19522361]

- Gordon CR, Spitzer O, Doweck I, Shupak A, Gadoth N. The vestibulo-ocular reflex and seasickness susceptibility. *J Vestib Res.* 1996; 6:229–233. [PubMed: 8839819]
- Graybiel A, Wood CD. Rapid vestibular adaptation in a rotary environment by means of controlled head movements. *Aerosp Med.* 1969; 40:638–643. [PubMed: 5305841]
- Graybiel A, Miller EF 2nd, Homick JL. Individual differences in susceptibility to motion sickness among six Skylab astronauts. *Acta Astronaut.* 1975; 2:155–174. [PubMed: 11841091]
- Graybiel, A.; Miller, EF.; Homick, JL. Experiment M-131. Human vestibular function. In: Johnston, RS.; Dietlein, LF., editors. Biomedical results from Skylab. Section II. Washington D.C: US Government Printing Office (NASA SP-77); 1977. p. 74-103.
- Guedry FE. Orientation of the rotation axis relative to gravity: its influence on nystagmus and the sense of rotation. *Acta Otolaryngol.* 1965; 60:30–48. [PubMed: 14337956]
- Guedry, FE. Psychophysics of vestibular sensation. In: Kornhuber, HH., editor. Handbook of sensory physiology. Vol. vol 6. New York: Springer, Berlin, Heidelberg; 1974. p. 3-154.
- Guedry FE, Benson AJ. Coriolis cross-coupling effects: Disorienting and nauseogenic or not? *Aviat Space Environ Med.* 1978; 49:29–35. [PubMed: 304719]
- Haslwanter T, Jaeger R, Mayr S, Fetter M. Three-dimensional eye-movement responses to off-vertical axis rotations in humans. *Exp Brain Res.* 2000; 134:96–106. [PubMed: 11026731]
- Hecht H, Kavelaars J, Cheung CC, Young LR. Orientation illusions and heart-rate changes during short-radius centrifugation. *J Vest Res.* 2001; 11:115–127.
- Hettinger JL, Berbaum KS, Kennedy RS, Dunlap WP, Nolan MD. Vection and simulator sickness. *Military Psychol.* 1990; 2:171–181.
- Hoffer ME, Gottshall K, Kopke RD, Weisskopf P, Moore R, Allen KA, Wester D. Vestibular testing abnormalities in individuals with motion sickness. *Otol Neurotol.* 2003; 24:633–636. [PubMed: 12851557]
- Holstein GR, Martinelli GP, Cohen B. Ultrastructure of GABA-immunoreactive vestibular commissural neurons related to velocity storage in the monkey. *Neuroscience.* 1999a; 93:171–181. [PubMed: 10430481]
- Holstein GR, Martinelli GP, Wearne S, Cohen B. Ultrastructure of vestibular commissural neurons related to velocity storage in the monkey. *Neuroscience.* 1999b; 93:155–170. [PubMed: 10430480]
- Igarashi M, Kobayashi K. Space motion sickness and space vestibulology. *J Uoeh.* 1985; 7 Suppl:228–236. [PubMed: 3874411]
- Irwin J. The pathology of sea-sickness. *Lancet.* 1881; 2:907–909.
- Johnson WH, Sunahara FA, Landolt JP. Importance of the vestibular system in visually induced nausea and self-vection. *J Vestib Res.* 1999; 9:83–87. [PubMed: 10378179]
- Katz E, de Jong JMBV, Büttner-Ennever JA, Cohen B. Effects of midline medullary lesions on velocity storage and the vestibulo-ocular reflex. *Exp Brain Res.* 1991; 87:505–520. [PubMed: 1783021]
- Kucharczyk, J.; Stewart, DJ.; Miller, AD. Nausea and vomiting, recent research and clinical advances. Boca Raton-Ann Arbor, Boston, London: CRC Press; 1991.
- Kushiro K, Dai M, Kunin M, Yakushin SB, Cohen B, Raphan T. Compensatory and orienting eye movements induced by off-vertical axis Rotation (OVAR) in monkeys. *J Neurophysiol.* 2002; 88:2445–2462. [PubMed: 12424285]
- Lackner JR, DiZio P. Angular displacement perception modulated by force background. *Exp Brain Res.* 2009; 195:335–343. [PubMed: 19381620]
- Lackner JR, Graybiel A. The effective intensity of Coriolis, cross-coupling stimulation is gravito-inertial force dependent: implications for space motion sickness. *Aviat Space Environ Med.* 1986; 57:229–235. [PubMed: 3485968]
- Matsnev EI, Yakovleva IY, Tarasov IK, Alekseev VN, Kornilova LN, Mateev AD, Gorgiladze GI. Space motion sickness: phenomenology, countermeasures, and mechanisms. *Aviat Space Environ Med.* 1983; 54:312–317. [PubMed: 6847567]
- McCauley, ME.; Royal, JW.; Wylie, CP.; O'Hanlon, JF.; Mackie, RR. Vol. vol 39. Santa Barbara, California: Human Factors Research, Inc; 1976. Motion sickness incidence: Exploratory studies of habituation, pitch and roll and the refinement of a mathematical model. Technical Report 1733-2

- Money KE. Biological effects of space travel. *Can Aeronaut Space*. 1981; J 27:195–201.
- O'Hanlon JF, McCauley ME. Motion sickness incidence as a function of the frequency of acceleration of vertical sinusoidal motion. *Aerospace Med*. 1974; 45:366–396. [PubMed: 4821729]
- Oman CM. A heuristic mathematical model for the dynamics of sensory conflict and motion sickness. *Acta Otolaryngol*. 1982; 392 (Suppl.):1–44.
- Putcha L, Berens KL, Marshburn TH, Ortega HJ, Billica RD. Pharmaceutical use by U.S. astronauts on space shuttle missions. *Aviat Space Environ Med*. 1999; 70:705–708. [PubMed: 10417009]
- Raphan T, Schnabolk C. Modeling slow phase velocity generation during off-vertical axis rotation. *Ann NY Acad Sci*. 1988; 545:29–50. [PubMed: 3149166]
- Raphan T, Sturm D. Modelling the spatiotemporal organization of velocity storage in the vestibuloocular reflex by optokinetic studies. *J Neurophysiol*. 1991; 66:1410–1420. [PubMed: 1761990]
- Raphan T, Dai M, Cohen B. Spatial orientation of the vestibular system. *Ann N Y Acad Sci*. 1992; 656:140–157. [PubMed: 1599139]
- Reason, JT.; Brand, JJ. Motion sickness. London: Academic Press; 1975.
- Reisine H, Raphan T. Neural basis for eye velocity generation in the vestibular nuclei during off-vertical axis rotation. *Exp Brain Res*. 1992; 92:209–226. [PubMed: 1493862]
- Schnabolk C, Raphan T. Modelling 3-D slow phase velocity estimation during off-vertical axis rotation (OVAR). *J Vest Res*. 1992; 2:1–14.
- Shupak A, Kerem D, Gordon C, Spitzer O, Mendelowitz N, Melamed Y. Vestibulo-ocular reflex as a parameter of seasickness susceptibility. *Ann Otol Rhinol Laryngol*. 1990; 99:131–136. [PubMed: 2301869]
- Solomon D, Cohen B. Stabilization of gaze during circular locomotion in light; I. Compensatory head and eye nystagmus in the running monkey. *J Neurophysiol*. 1992a; 67:1146–1157. [PubMed: 1597704]
- Solomon D, Cohen B. Stabilization of gaze during circular locomotion in darkness; II. Contribution of velocity storage to compensatory eye and head nystagmus in the running monkey. *J Neurophysiol*. 1992b; 67:1158–1170. [PubMed: 1597705]
- Sturm, D.; Raphan, T. IEEE Proceedings of Northeast Bioengineering. 1988. Modelling the three dimensional structure of velocity storage in the vestibulo-ocular reflex (VOR).
- Sugita-Kitajima A, Koizuka I. Somatosensory input influences the vestibulo-ocular reflex. *Neurosci Lett*. 2009; 463:207–209. [PubMed: 19660526]
- Thornton WE, Uri JJ. Oculomotor function during space flight and susceptibility to space motion sickness. *Acta Astronaut*. 1991; 23:53–61. [PubMed: 11537148]
- Ventre-Dominey J, Luyat M, Denise P, Darlot C. Motion sickness induced by otolith stimulation is correlated with otolith-induced eye movements. *Neuroscience*. 2008; 155:771–779. [PubMed: 18620028]
- Wang SC, Chinn HI. Experimental motion sickness in dogs. Importance of labyrinth and vestibular cerebellum. *Am J Physiol*. 1956; 185:617–623. [PubMed: 13340001]
- Wearne S, Raphan T, Cohen B. Nodulo-uvular control of central vestibular dynamics determines spatial orientation of the angular vestibulo-ocular reflex (aVOR). *Ann NY Acad Sci*. 1996; 781:364–384. [PubMed: 8694428]
- Wearne S, Raphan T, Cohen B. Contribution of vestibular commissural pathways to velocity storage and spatial orientation of the angular vestibuloocular reflex. *J Neurophysiol*. 1997; 78:1193–1197. [PubMed: 9307151]
- Wearne S, Raphan T, Cohen B. Control of spatial orientation of the angular vestibuloocular reflex by the nodulus and uvula. *J Neurophysiol*. 1998; 79:2690–2715. [PubMed: 9582239]
- Wood SJ. Human otolith-ocular reflexes during off-vertical axis rotation: effect of frequency on tilt-translation ambiguity and motion sickness. *Neurosci Lett*. 2002; 323:41–44. [PubMed: 11911986]
- Yates BJ. Vestibular influences on the sympathetic nervous system. *Brain Res Rev*. 1992; 17:51–59. [PubMed: 1638275]
- Yates BJ, Miller AD. Physiological evidence that the vestibular system participates in autonomic and respiratory control. *J Vest Res*. 1998; 8:17–25.

- Yates BJ, Jian BJ, Cotter LA, Cass SP. Responses of vestibular nucleus neurons to tilt following chronic bilateral removal of vestibular inputs. *Exp Brain Res*. 2000; 130:151–158. [PubMed: 10672468]
- Yokota JI, Reisine H, Cohen B. Nystagmus induced by electrical microstimulation of the vestibular and prepositus hypoglossi nuclei in the monkey. *Exp Brain Res*. 1992; 92:123–138. [PubMed: 1486947]
- Young LR, Henn V. Nystagmus produced by pitch and yaw rotation of monkey about non-vertical axes. *Forsch Zool*. 1975; 23:235–246.
- Young LR, Hecht H, Lyne L, Sienko K, Cheung C, Kavelaars J. Artificial gravity: head movements during short-radius centrifugation. *Acta Astronautica*. 2001; 49:215–226. [PubMed: 11669111]

Fig. 1. Experimental paradigm. **a** Horizontal slow phase eye velocity. **b** Body position re gravity. The *baseline* represents the body upright position. **c** Skin conductance in microsiemens. **d** Chair velocity. The test began with the chair upright, rotating to the right at 60 $^{\circ}/s$ (acc. 200 $^{\circ}/s^2$). The axis of rotation, at 72 s after the per-rotatory nystagmus had died away, was tilted in 15 s to 30 $^{\circ}$ (**b**). The steady state bias (6.25 $^{\circ}/s$) and peak velocity modulation (8.57 $^{\circ}/s$) were obtained from a sine fit of the data ($6.25\sin(2\pi t/6+0.35) + 8.57$) as shown by the *black sinusoidal line* in **a**. Heavy sweating was reflected by a quick rise in the skin conductance (**c**). At that point, the subject reported a motion sickness score of 10

Fig. 2.
a Horizontal bias velocities induced by different tilts of the axis of rotation during OVAR. **b** Bias velocity as a function of rotation velocity during OVAR. *Error Bars* = ± 1 SD

Fig. 3. Motion sickness scores (ordinate) over time (abscissa) after reaching the final tilt angle in nine subjects. Data were from the test with 30° tilt of the axis of rotation and a rotational velocity of 60°/s

Fig. 4. Individual motion sickness sensitivity (MSS) as a function of the disparity in $^{\circ}/s$ (abscissa). Each of the dots represents one of the six test conditions. The slopes and correlation coefficients (R) for each set of data are shown

Figure 5. Motion sickness sensitivity (MSS, red line) and bias velocity (Bias Vel, blue dashed line) as a function of rotational velocity during OVAR around an axis tilted 30°. MSS and bias velocity peaked at the same rotational velocity (60°/s). Error bar = ± 1 SD

Fig. 6.

a Peak-to-peak modulation of horizontal slow phase eye velocity as a function of rotational velocity during OVAR at a tilt angle of 30° . **b** Peak-to-peak modulation of horizontal slow phase eye velocity as a function of angles of tilt of the axis of rotation at 10° , 20° , and 30° . The error bar = ± 1 SD

Fig. 7. Individual motion sickness sensitivity (MSS) as a function of modulations in peak-to-peak horizontal eye velocity in °/s (abscissa). Each of the dots represents one of the six test conditions. The slopes and correlation coefficients (R) for each set of data are shown

CONCEPTUAL MODEL OF MOTION SICKNESS GENERATION DURING OVAR

Fig. 8.
Conceptual model of motion sickness generation during OVAR

Fig. 9.

Simulation of motion sickness generation during OVAR. The simulations were run for 100 s using a rotational velocity about a vertical axis. The axis of rotation was then tilted over 15 s to a given angle. The tilt angles were 10°, 20°, 30°, and the rotational velocities were 30°/s, 60°/s, 120°/s and 150°/s. The vertical extent of the aVOR responses in (b) and (f) were truncated to have a better resolution of the OVAR responses. See text for detailed description of the simulated responses at a fixed tilt angle and different velocities (a–d) and a fixed rotational velocity at different tilt angles (e–h). The simulation time constant of the motion sickness integrator was 50 s

Fig. 10.

a Model for estimation of head velocity ($\hat{\omega}$) during OVAR, with the pattern velocity estimation formula. **b** Neural network implementation of the model given in **a**. **c** Model predictions of the velocity estimation versus tilt angle for five simulated head velocities. The velocities are: 0°/s (*open squares*), 20°/s (*closed circles*), 40°/s (*closed squares*), 60°/s (*open circles*), and 80°/s (*open triangles*). The training tilts are 0, 30, 50, and 90°. The time delay is 0.75 s

Table 1

Average time constants and gains of the aVOR from the nine subjects before each of the six OVAR tests

OVAR Test	Time constant ± 1 SD	Gain ± 1 SD
1	15.4 $\pm$ 3.7	0.67 $\pm$ 0.08
2	13.8 $\pm$ 3.3	0.69 $\pm$ 0.07
3	14.1 $\pm$ 5.1	0.72 $\pm$ 0.09
4	13.2 $\pm$ 3.7	0.68 $\pm$ 0.08
5	14.2 $\pm$ 4.3	0.71 $\pm$ 0.07
6	13.4 $\pm$ 3.5	0.69 $\pm$ 0.10