

MOTION SICKNESS INDUCED BY OTOLITH STIMULATION IS CORRELATED WITH OTOLITH-INDUCED EYE MOVEMENTS

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Abstract—This article addresses the relationships between motion sickness (MS) and three-dimensional (3D) ocular responses during otolith stimulation. A group of 19 healthy subjects was tested for motion sickness during a 16 min otolith stimulation induced by off-vertical axis rotation (OVAR) (constant velocity 60°/s, frequency 0.16 Hz). For each subject, the MS induced during the session was quantified, and based on this quantification, the subjects were divided into two groups of less susceptible (MS⁻), and more susceptible (MS⁺) subjects. The angular eye velocity induced by the otolith stimulation was analyzed in order to identify a possible correlation between susceptibility to MS and 3D eye velocity. The main results show that: (1) MS significantly correlates in a multiple regression with several components of the horizontal vestibular eye movements i.e. positively with the velocity modulation ($P < 0.01$) and bias ($P < 0.05$) of the otolith ocular reflex and negatively with the time constant of the vestibulo-ocular reflex ($P < 0.01$) and (2) the length of the resultant 3D eye velocity vector is significantly larger in the MS⁺ as compared with the MS⁻ group.

Based on these results we suggest that the CNS, including the velocity storage mechanism, reconstructs an eye velocity vector modulated by head position whose length might predict MS occurrence during OVAR. © 2008 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: motion sickness, otolithic function, eye velocity vector, OVAR, human.

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Abbreviations: ANOVA, analysis of variance; CCW, counterclockwise; cVOR, canal vestibulo-ocular reflex; CW, clockwise; H, horizontal component; HQ, History Questionnaire; LED, light emitting diode; MS, motion sickness; MSGR, motion sickness growth rate; MSQ, Motion Sickness Questionnaire; ND, nose down; NU, nose up; OVAR, off-vertical axis rotation; oVOR, otolith vestibulo-ocular reflex; VOG, video-oculography; VOR, vestibulo-ocular reflex; VSM, velocity storage mechanism; 3D, three-dimensional.

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Motion sickness (MS) typically occurs during unusual body motions which induce discrepancies between sensory-motor signals, so that messages about motion in the environment do not reflect the physical reality. The motion signals from different sensory modalities (visual, vestibular, proprioceptive) and motor systems (efferent copy) can conceivably mismatch, either with other signals or with internal representations of expected motion variables (Reason and Brand, 1975; Leigh and Daroff, 1985; Bles, 1998; Bles et al., 1998; Bos and Bles, 1998, 2002; De Graaf et al., 1998; Guedry et al., 1998; Warwick-Evans et al., 1998; Yates et al., 1998).

Central pathways combine the signals from the various sensory organs (semicircular canals, otoliths, vision) and compute estimates of the kinematic variables (of head and gaze rotational and translational accelerations and velocities in space, and of head and gaze orientations with respect to gravity). These visuo-vestibular pathways constitute an internal neural network traditionally referred to as the “velocity storage mechanism” (VSM) (Robinson 1975, 1977; Raphan et al., 1977). During off-vertical axis rotation (OVAR) at constant velocity, the orientation of the head with respect to gravity changes continuously and gravity sweeps the otolithic maculae receptors. The VSM computes estimates of head velocity including: (1) an estimate of head rotational velocity that in turn drives a compensatory mean eye velocity called the “bias” of the steady-state nystagmus and (2) an estimate of head translational velocity, although no actual translation occurs, that gives rise to the horizontal modulation of the steady-state nystagmus (Hain, 1986; Darlot et al., 1988; Darlot and Denise, 1988; Denise et al., 1988; Raphan and Schnalblock, 1988; Angelaki et al., 1992; Tweed et al., 1994; Angelaki and Hess, 1995, 1996).

Recently, using cross-coupling vestibular stimulation, it has been proposed that MS is related to the spatio-temporal properties of the VSM. By tilting the head while rotating at constant velocity, subjects can experience serious MS symptoms whose strength is associated with the change in compensatory eye velocity, reflecting the change in estimated head velocity (Dai et al., 2003). The eye axis of rotation tends to be re-oriented toward gravity in relation to a dumping of the velocity storage integrator (Angelaki and Hess, 1994; Raphan and Cohen, 2002; Wearne et al., 1999; Sheliga et al., 1999; Bockisch et al., 2003; Dai et al., 2003). Accordingly, Quarck et al. (1998) found a correlation between MS and the canal-ocular reflex time constant and thus suggested that central vestibular integration i.e. the VSM, by increasing low frequency vestibular inputs, would favor MS. MS can arise in most normal people and

also in pathological conditions. Hence, the link between MS and vestibular function has been revealed by labyrinthectomy that reduces or abolishes MS occurrence (Cheung et al., 1991), although it is not clear whether this effect is due directly to the suppression of the vestibular inputs or indirectly to the resulting decrease in activity of the VSM. In aerospace research, studies in astronauts demonstrated a link between some characteristics of the VSM and susceptibility to space MS (DiZio and Lackner, 1991; Cheung et al., 1995; Clément et al., 1995; Lackner and DiZio, 2006 as a review). Thus, DiZio and Lackner (1991) reported that “the greater the capacity for velocity storage and the more precipitous the dumping that occurs during post-rotatory head tilts in 1G, the more susceptible an individual is when moving about in parabolic flight.” Likewise, the level of MS, quantitatively estimated, has been correlated to the incoherence between the central representations of the kinematic variables as estimated by means of mathematical models of the VSM (Oman 1982, 1990; Zupan, 1995; Eskiizmiriler, 1999). Nevertheless, a possible behavioral relationship between MS and eye movements, which could provide indirect insight into VSM function and have a predictive value concerning susceptibility to MS, remains to be further investigated.

OVAR has been proven to be a useful method in studying MS susceptibility and symptomatology, including the underlying CNS mechanisms (Graybiel and Miller, 1970). Therefore, in the current study, healthy subjects were tested for MS during OVAR stimulation. According to their quantified susceptibility to MS during OVAR, they were separated into two groups of less susceptible (MS−), and more susceptible (MS+) subjects. The three-dimensional (3D) eye velocity vector induced in response to OVAR was measured, with the objective of discovering a regular relationship between susceptibility to MS and characteristics of the eye velocity responses to this unusual experimental vestibular stimulation.

EXPERIMENTAL PROCEDURES

Subjects

A group of 19 healthy subjects (mean age=27.5; S.D.=6; 10 males, 9 females) volunteered to participate in the experiment. All were free of any vestibular and ocular pathologies and of neurological diseases. Prior to any vestibular testing, they were fully informed about the possible nauseating effects of the examination and gave their consent to participate in the study. The experimental protocols were duly approved by the local ethic committee at Lyon Hospital (CCPRB Lyon A, Hôtel-Dieu, Hospices Civils, No. Rg/FL-2001-007-62A).

Experimental setup

Subject were comfortably seated and secured in a rotating chair, driven by a torque motor, placed on a platform that could be tilted by hydraulic jacks placed at one side. The mid-point between the two ears was positioned and maintained by a concave head rest and a frontal support along the axis of rotation. The head rest was tilted 15° nose-down, in order to position the horizontal semicircular canal parallel to the earth horizontal plane. The 3D position of the left eye was recorded by video-oculography (VOG, SensoMotoric Instruments, Teltow, Germany). The VOG system used a

miniaturized charge coupled device (CCD) video sensor fixed on a head-mounted assembly. To provide a constant light distribution over the full image, three infrared light emitting diodes (LED) were mounted concentrically with the camera optics. The VOG signals were amplified before passing through slip rings, placed over the head. These VOG signals were then processed (sample frequency=50 Hz) on a PC computer and stored both on the computer and on a digital recorder for further off-line analysis.

Facing the chair at the rest initial position (zero angle of rotation), was an eye position calibration panel consisting of horizontal and vertical rows of LEDs, spaced at 10° intervals.

Protocol

Calibration. A VOG calibration was performed with horizontal and vertical saccades elicited by visual targets (LEDs) at 10° and 20° right and left, up and down.

Vestibular stimulation. After 1 min of spontaneous eye movement recording, the subjects underwent two successive vestibular tests in complete darkness.

Velocity step rotation. The chair was accelerated about an earth vertical axis, up to a constant velocity of 60°/s (acceleration: 100°/s²), and after 90 s of rotation the chair was stopped (deceleration: 100°/s²). This allowed testing of the vestibulo-ocular reflex (VOR) arising from stimulation of the semicircular canals, in the two directions of rotation rightward (clockwise: CW) and leftward (counterclockwise: CCW). At the beginning of the trial, the per-rotatory nystagmus was recorded in response to chair acceleration and at the end, the post-rotatory nystagmus was recorded in response to deceleration, after the chair had stopped.

OVAR. While rotating at constant velocity (60°/s to the left), the axis of rotation was tilted over 2 s to 12° off-vertical. Based on previous OVAR studies (Quarck et al., 2000), the vestibular nystagmus was recorded for 120 s allowing the otolith responses to be assessed, and thereafter for 840 s (14 min) of steady-state otolith responses (plateau). Then the chair was tilted back to its starting position and rotated around the earth vertical axis for another 120 s to allow the otolith responses to subside and finally the chair was stopped (Fig. 1).

In all the subjects, the experimental series was the following: two VOR sessions (CW/CCW directions in balanced order) followed by the OVAR session. In order to render the examination only moderately nauseogenic, the otolith-ocular function was tested in a single OVAR session (intertilt duration: 16 min) at a small tilt angle (12°) and in the low frequency range (0.16 Hz).

MS and motion perception evaluation

Prior to the experiment, the sensitivity of each subject to MS was evaluated by means of two questionnaires that record the individual exposure and the occurrence of illness to motion in different forms of transport at different life periods: (1) during the past year for the History Questionnaire (HQ, adapted from Alexander et al., 1945) and (2) during the last 10 years and during the childhood (<12 years) for Motion Sickness Questionnaire (MSQ, Reason and Brand, 1975).

Then, during each experimental session, the occurrence and gradation of the MS signs induced by OVAR were estimated based on the Graybiel et al. (1968) MS scaling. The level of MS was monitored every 120 s by asking the subject to report on a scale between 0 and 10 for each of the following signs: sleepiness, headache, hypersalivation, perspiration, gastric discomfort (gastric awareness), nausea. Gradation 0 corresponded to no sign, 5 to a moderate level and 10 to the strongest level of sensation or sign. Subjects could easily estimate the gradation of their sensations throughout the test, and were allowed to stop the test at any time when feeling too dizzy or nauseated. In no subject did the discomfort ever reach the point of vomiting. In three subjects (17, 18, 19), because of a rapid onset of major MS signs,

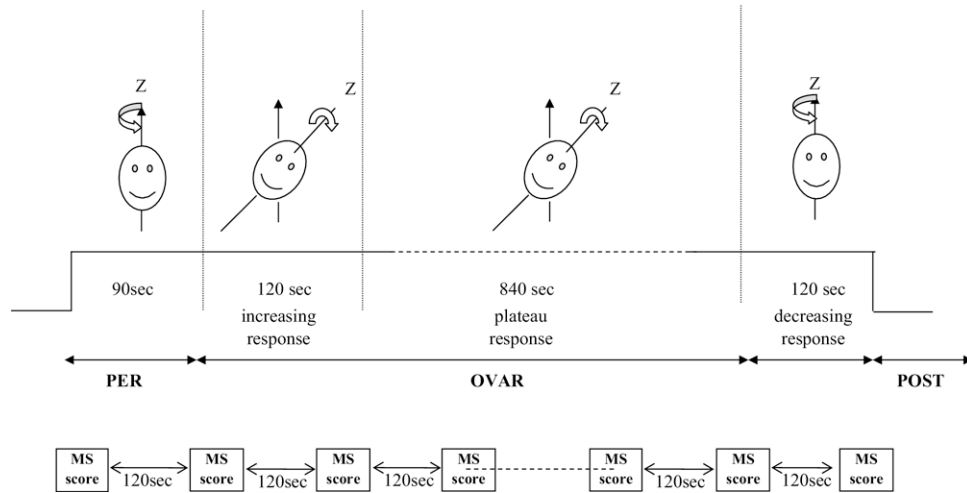


Fig. 1. Schematic representation of the experimental paradigm, showing the different phases of the OVAR vestibular stimulation and the timing of the MS score measurements. PER: per-rotatory nystagmus elicited at the onset of the earth-vertical rotation. OVAR sub-divided in an increasing response period and a response plateau period. The decreasing response corresponds to the post-OVAR period after the chair is tilted back and then is rotating around the earth vertical axis. POST: post-rotatory nystagmus elicited at the offset of the earth-vertical rotation. MS scores are measured every 120 s up to the end of the subject rotation.

the chair was stopped within 2 min of OVAR stimulation. Their otolith-ocular movements never reached the steady-state, and consequently were not included in the eye movement analysis (see Table 1).

After the OVAR session, the subject was asked for his/her perception of self-movement in terms of the direction, the axis of the subjective rotation and the tilt sensation.

Table 1. MS scores measured with the HQ, the MSQ and experimental MS scores measured during OVAR stimulation, for each subject of each group (MS++: MS+: more susceptible group. MS-: less susceptible group)

MS group	1	HQ	MSQ	Score for nausea sign	Total MS score	MSGR	T
MS+	1	7	45	7	21	10.8	194
MS+	2	2	27.8	7	25	7.6	331
MS+	3	4	77.9	5	21	7.4	285
MS+	4	10	73	6	17	6.8	251
MS+	5	3	76	6	21	6.0	349
MS+	6	5	39	6	16	6	267
MS+	7	6	37.3	5	12	3.1	386
MS+	8	2	11.3	4	28	2.9	960
MS+	9	0	19.8	5	8	1.8	451
MS-	10	7	53.7	5	11	1.1	960
MS-	11	5	59	1	5	0.6	960
MS-	12	3	39.8	0	5	0.52	960
MS-	13	5	34.5	2	3	0.3	960
MS-	14	10	19	0	0	0	960
MS-	15	1	8.6	0	0	0	960
MS-	16	0	0	0	0	0	960
na	17	22	15.5	7	24	41.4	58
na	18	0	0	4	22	24.4	90
na	19	24	98	5	7	6.5	108

The experimental MS scores are represented for the nausea sign, the sum of the six MS signs measured at the end of OVAR, the index MSGR and the bearable duration of the OVAR session. na, no eye movements analysis.

Data analysis

Eye velocity analysis. Eye movements were analyzed off-line, by replaying the eye images from the digital video tape. Using geometric and statistical filter methods, the image processor reconstructed the pupil center coordinates from a circular fit along the borders of the identified (thresholded) pupil area. The horizontal and vertical eye positions were measured on the position of the center of the pupil. The torsional position was derived from a circular ring segment selected on the iris. To evaluate torsional eye movements between two video images, the horizontal shift of the previously selected iris segment was analyzed, using a cross-correlation technique. Once the adequate parameters had been adjusted, the images were processed over several cycles and the 3D eye positions were extracted and stored on the computer. Finally the 3D eye position signals were analyzed by means of an interactive software SAMO (Denise et al., 1996) that processed eye movement velocity by using the two-point central difference algorithm (50 ms step size). Quick phases were then removed, by an algorithm using velocity and acceleration thresholds.

3D eye movements were expressed in a head-centered coordinate system with the +X (roll/torsion) axis along the forward naso-occipital axis, the +Y (pitch/vertical) axis along the interaural axis to the left and the +Z (yaw/horizontal) axis along the head vertical axis. Thus, the positive eye velocity and position values indicated respectively CW, downwards and leftwards eye movements. The instantaneous velocity vectors were computed in the yaw/horizontal, roll/torsional and pitch/vertical planes from Fick coordinates according to Haslwanter (1995) and the length of resultant 3D velocity vector \dot{E} (equation 1) and its angle α to the head axis (Z) (equation 2) were calculated:

$$\|\dot{E}\| = \sqrt{\dot{E}(z)^2 + \dot{E}(y)^2 + \dot{E}(x)^2} \quad (1)$$

$$\alpha \dot{E}(\text{rad}) = \frac{\text{ACOS}(\dot{E}(z))}{\sqrt{\dot{E}(z)^2 + \dot{E}(y)^2 + \dot{E}(x)^2}} \quad (2)$$

z=horizontal velocity vector
y=vertical velocity vector
x=torsional velocity vector

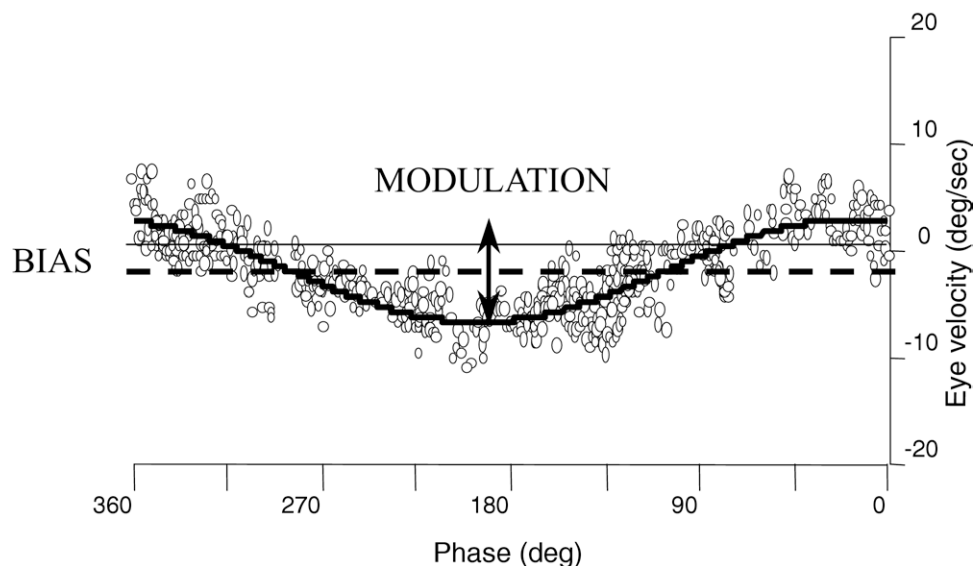


Fig. 2. Method of calculation of the bias and modulation of the eye velocity induced by OVAR. The ocular slow phase velocities are plotted and superimposed over 15 cycles of chair rotation. Parameters are estimated by least square fitting of a sinusoid (MODULATION: thick line) plus offset (BIAS: dotted line) on the values of slow phase velocities.

Eye movement parameters. Different parameters were quantified based on the nystagmus slow phase velocity (SPV) and position as following.

Per- and post-rotatory responses. VOR gain was calculated as the ratio between maximal slow phase velocity and constant chair velocity. VOR time constant was measured as the time when the area under the slow phase velocity curve reaches 63% of the total area (Denise et al., 1996). For each parameter, the mean value between the two per- and post-rotatory slow phase responses induced in the same direction was calculated to be used for further statistical analysis.

OVAR. The velocity and position of nystagmus slow phases were computed over 15 cycles of the steady-state response and superimposed. The parameters of the slow eye movements induced in each horizontal, vertical and torsional plane were ex-

tracted by least square fitting a sinusoid (modulation) plus offset (bias) on the value of slow phase velocity and position (Denise et al., 1996), as shown in Fig. 2. The bias, and the modulation amplitude and phase, were then calculated on the velocity and the position ocular traces in each plane.

As previously described, we calculated the instantaneous velocity vectors obtained after the Fick to Listing transformation in the yaw/horizontal, roll/torsional and pitch/vertical planes, the length of the vectorial sum or the resultant 3D velocity vector \dot{E} (equation 1) and its angle α to the head axis (equation 2). These parameters were calculated at different head positions: nose up (NU), left ear up (LEU), nose down (ND) and left ear down (LED). In one subject (Table 2, Subject 3), the eye movements in the roll plane were not analyzed because of a poor noisy quality of the ocular signal.

Table 2. Mean eye velocity ($^{\circ}/s$) of the OVAR bias (B), modulation (M) and phase measured in each plane, for each subject of each MS+ and MS- group

MS Group	Case	MSGR	cVOR		Horizontal oVOR			Vertical oVOR			Torsional oVOR		
			Gain	TC	B	M	Phase	B	M	Phase	B	M	Phase
MS+	1	10.8	0.53	13.6	0.75	3.45	173	-0.29	0.36	27	-0.35	1.4	-92
MS+	2	7.55	0.28	16	1.88	3.1	81	-0.01	0.79	13	-0.85	0.8	-149
MS+	3	7.37	0.65	13.7	6.23	2.58	-5	3.01	0.69	57	-	-	-
MS+	4	6.77	0.54	22.4	1.12	4.87	70	-1.12	1.91	-170	0.79	0.72	-154
MS+	5	6.02	0.47	17.4	2.63	4.13	1	-1.38	0.22	132	-0.32	0.89	156
MS+	6	5.99	0.48	9.55	2.27	1.88	-35	0.69	1.56	-85	-0.12	1.81	36
MS+	7	3.11	0.38	12.6	-0.7	2.75	-28	1.58	1.61	-37	0.09	0.87	44
MS+	8	2.92	0.25	10.9	1.96	1.17	-63	0.35	0.66	-47	-0.32	0.53	27
MS+	9	1.77	0.70	16.3	1.15	2.6	171	-3.01	1.69	-173	0.42	2.27	-38
MS-	10	1.15	0.88	11.9	-1.5	1.92	-11	-0.1	1.02	-23	0.27	0.02	60
MS-	11	0.52	0.80	17.4	-0.6	2.6	-129	-1.23	1.5	-101	-0.6	0.27	-128
MS-	12	0.52	0.81	18.1	1.99	3.11	54	-0.55	2.49	50	0.22	1.24	-167
MS-	13	0.31	0.43	11.5	0.05	1.91	-78	-0.6	0.67	-59	0.16	0.98	56
MS-	14	0	0.57	15.5	0.68	1.2	-122	-0.24	2.36	-84	0.27	0.82	-35
MS-	15	0	0.52	16.1	-0.8	1.68	142	0.25	0.73	-7	-0.24	2.07	171
MS-	16	0	0.64	19.3	4	1.1	-3	0.76	2.18	45	-1.03	2.37	-171

MSGR, MS score measured during OVAR; TC, cVOR time constant. (In Subject 3, torsional eye movements were not analyzed.)

MS evaluation. MS was scaled from 0 to 36 using the HQ (adapted from Alexander et al., 1945) and, from 0 to 180 using the MSQ (Reason and Brand, 1975).

MS can be quantified in terms of multiple parameters including (1) the duration (T) of the bearable stimulation, determined as the time when the intensity of the subject’s malaise induced him/her to stop the experiment, (2) the nausea score, and (3) the sum of the scores of the six MS signs recorded when the MS was the greatest i.e. just before the stimulation stopped. We observed a large variability in subject’s tolerance of the malaise as with the same MS score, some subjects could maintain a long duration of the OVAR session and others only a short duration. In order to normalize the MS signs with respect to the duration of bearable stimulation, we calculated an index that we called the motion sickness growth rate (MSGR) as a function of the subjective scale for the six symptoms and the bearable duration of the stimulation:

$$MSGR = \sum S \times 100 / T$$

$\sum S$ = sum of scaled symptoms (theoretical max = 60)

T = duration of the stimulation in seconds

MSGR thus takes into account not only the level of MS intensity, but also the duration required to attain that level of MS intensity, and consequently provides a rate of MS susceptibility per unit time. The more the subject is susceptible to MS, the higher will be the MSGR.

Statistical analysis

Statistical analysis was performed on the different parameters extracted from the eye velocity and position in each plane (horizontal, vertical and torsional). As the distribution of the variables (MSGR, eye velocity, time constant) followed a normal distribution (Kolmogorov-Smirnov test, $P > 0.05$), we used parametric statistical tests.

MS evaluation. As shown in Fig. 3, by considering nausea, maximum MS signs and OVAR bearable duration, two groups of subjects could be distinguished: (1) a group of less susceptible subjects (MS-; $n=7$) who performed the whole stimulus session with no interruption and none, or very weak, MS signs (MSGR < 1.5), and a group of more susceptible subjects (MS+; $n=12$) who could not undergo the entire OVAR session and/or

presented early and significant MS signs (MSGR > 1.5) (Table 1). To compare the level of MS between these groups, an analysis of variance (one way multivariate ANOVA) was performed on the dependent MS parameters (MS signs, nausea, T, MSGR) using as the between subject factor the Groups (MS+, MS-). A Bonferroni post hoc comparison was applied to the MS parameters. Moreover, the MS scores including those issued from the questionnaires HQ and MSQ, were compared by using a Pearson product-moment correlation analysis.

Eye movements parameters. The MS score (MSGR) and the eye movement parameters (VOR gain and TC, OVAR modulation and bias) were correlated by using Pearson product-moment correlation and multiple regression analysis. An ANOVA (one way univariate ANOVA) was used to analyze the differences in the eye movement parameters between the subject Groups (MS+, MS-). In order to evaluate the effects of head position on eye velocity vectors in each MS group, we performed an ANOVA (one way repeated measures ANOVA) on the dependent MS parameter (MSGR) and the eye velocity vectors, using as a within-factor the Head Position and as a between-subjects factor the Groups (MS+, MS-).

Prior to any statistical comparison, the homogeneity of variance of the parameters in each group was assessed using a Levene test ($P > 0.05$). The Statistica software package was used to perform the statistical analysis. The significance level was set at a 95% confidence interval.

Due to a poor quality ocular signal (Subject 3), or a short OVAR duration related to a high MS susceptibility (Subjects 17, 18, 19), four subjects were excluded from the analysis, so that statistics were based on 15 from the 19 recorded subjects (MS- group: $n=7$ and MS+ group: $n=9$).

RESULTS

Movement sensation

The subjects described sensations similar to those previously reported by Denise et al. (1988): 25% of the subjects reported a sensation of being rotated in a cone whose axis was tilted or not, 50% a sensation of a cycloid-like movement i.e. a sensation of moving along a cone whose axis would describe a larger cone, others (19%) described a sensation of a tilted rotation. Very few subjects had the sensation of rotating around the earth vertical with occasional tilt (6%). There was no evidence of any relationship between the type of experienced sensation and susceptibility to MS.

MS susceptibility evaluation

Correlations were found between MSGR and MSQ ($r=0.53$, $P=0.029$) and MSGR and nausea ($r=0.84$, $P<0.001$). In contrast, the HQ scores were correlated only to the MSQ at $P=0.005$ ($r=0.65$). Susceptibility to MS during OVAR, was significantly different between the two MS groups (MS+ and MS-) as estimated for all the parameters (main group effect: $F(6,9)=57.7$, $P<0.001$) i.e. T, nausea, MS signs and MSGR at a significance level of $P<0.001$ for each one, after Bonferroni post hoc comparison. These parameters were altogether correlated either positively for MSGR, nausea and MS signs when compared with each other ($P<0.001$) or negatively for T when compared with MSGR, nausea and MS signs ($P<0.01$). In the following sections, we will describe the results mainly in terms of the MSGR

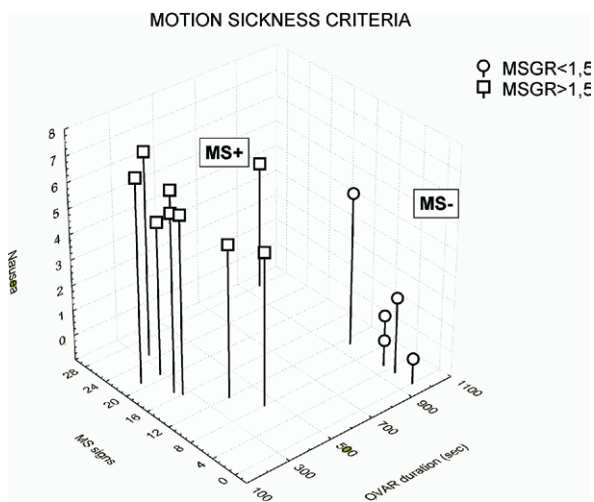


Fig. 3. 3D scatterplots showing for each subject the nausea score as a function of the total MS signs and the OVAR duration. It illustrates the dissociation of the subjects population into two MS groups: MS+ including the most susceptible subjects and MS- including the less susceptible subjects.

scale that is the MS rate as explained above in the Experimental Procedures.

MS susceptibility and vestibulo-ocular performance

Velocity bias and modulation and VOR time constant. Head rotation about earth-vertical axis (horizontal semicircular canal stimulation) induced a purely horizontal canal vestibulo-ocular reflex (cVOR). While rotating at constant velocity, a tilt of the rotation axis (OVAR) evoked 3D otolith vestibulo-ocular reflex (oVOR) responses (otolith stimulation) whose angular velocities could largely vary in the different head planes. The mean values of the eye velocity are reported in each plane and for each subject in Table 2.

Significant correlations between MSGR and angular eye velocities were found only for the horizontal component (H). A simple linear correlation analysis revealed a relation only between MSGR and the amplitude of H velocity modulation (Pearson $R^2=0.61$, $P=0.012$). No direct relation was found between H-cVOR time constant and MSGR (Pearson $R^2=0.05$, $P>0.05$). In contrast, multiple regression analysis demonstrated several significant correlates of MSGR ($r=0.86$; $R^2=0.75$; R^2 adjusted=0.66; $F(4,11)=8.2$ $P=0.0026$). The significant predicting variables were the H velocity modulation ($b=0.79$; $P=0.0013$), H velocity bias ($b=0.40$, $P=0.023$) and the H-cVOR time constant ($b=-0.57$, $P=0.008$). As shown in Fig. 4, MSGR increases as the modulation amplitude increase and the cVOR time constant decreases.

The ANOVA on H modulation velocity showed that the H modulation was marginally greater in the MS+ group than in the MS- group (main effect: $F(1,14)=4.35$, $P=0.055$) and this parameter was highly correlated to the VOR time constant only in the MS+ group (intra-group correlation: $r=0.88$, $P=0.0018$, $cov=3.8$).

During OVAR, the projection of the H of the gravity vector follows a sinusoidal progression with respect to the

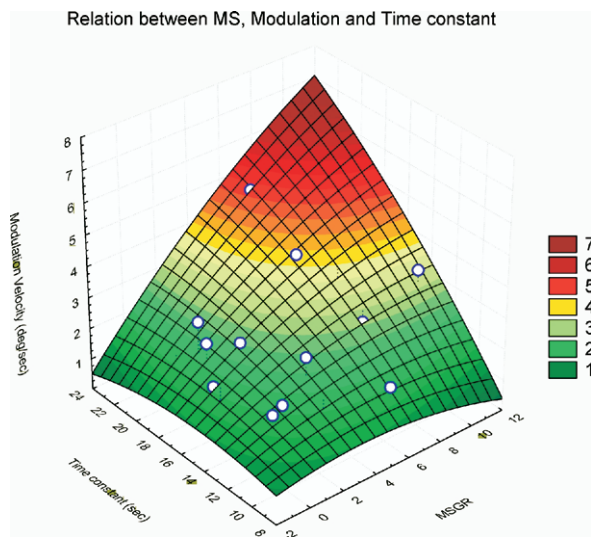


Fig. 4. 3D surface plot using a least square smoothing procedure that illustrates the relation between the MS susceptibility (MSGR), the modulation of the horizontal eye velocity and the VOR time constant.

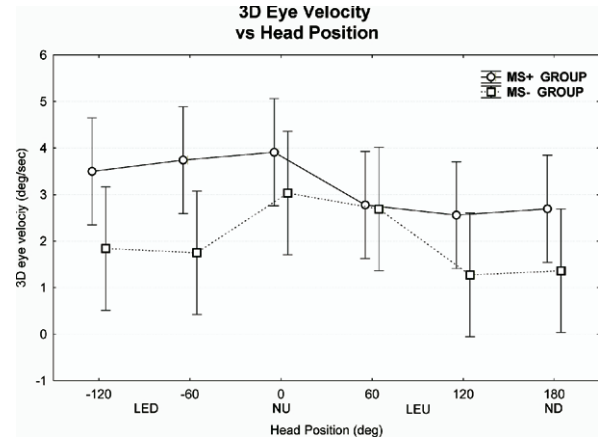


Fig. 5. Graph of the 3D eye velocity as a function of the head position, in each MS+ and MS- subjects group. Note only in MS+ group, the significant difference in 3D eye velocity mainly when head positions change from ND to NU. S.D. is represented by the bars.

head. To determine if H velocity elicited during OVAR follows the head position progression, we analyzed the eye velocity in terms of a sinusoidal function of head position. Thus, separately for each MS group, a sinusoid was fitted to the H eye velocity (H-Vel) as a function of head position (H) expressed by the following equation: $H\text{-Vel}=a+b\times\sin(H\times\pi/180+c)$. This sine model fits H-Vel only in the MS+ group, with the following significant regressors: $a=2.3$ at $P<0.002$, $b=2.1$ at $P=0.03$ and $c=20.7$ at $P<0.0001$. As revealed by the ANOVA, the fit of the head position related sine model to the data was significant in the MS+ group ($F=5$, $P=0.005$) and not in the MS- group ($F=1.07$, $P>0.05$). These results indicate that in MS+ group only, the H eye velocity is significantly more dependent on the changes in head position than in the MS- group.

Eye velocity vectors. Using the Fick to Listing transformation of the eye velocity (Haslwanter, 1995), the resultant 3D eye velocity vector was computed, and the angle it forms with the head axis was estimated, at each head position and in each MS group. As shown in Fig. 5, the length of the 3D eye velocity vector was greater in the MS+ group as compared with the MS- group (main Group effect: $F(1,72)=11.2$, $P=0.0013$). While independent of head position (Group \times Head position interaction effects: $F(5,72)=1.9$, $P>0.05$), this effect was more pronounced when the head was moving from the ND to the NU positions (see Fig. 5). Notably, at this latter head position, a clear correlation could be observed between the 3D eye velocity length and the MSGR (ND at 180 deg: $r=0.61$, $P=0.02$; LED at -120 deg: $r=0.66$, $P=0.01$; UP at -60 deg: $r=0.58$, $P=0.03$). The angle between the 3D eye velocity and the head axis did not vary significantly between the two MS groups (main Group effect: $F(1,71)=10.7$, $P=0.002$; Group \times Head position interaction effects: $F(5,71)=0.45$, $P>0.05$).

No significant correlation could be found between MSGR and any other parameters of the eye velocity and position, in the horizontal plane (including cVOR gain) or in the vertical nor in the torsional planes.

DISCUSSION

This study demonstrates a correlation between the susceptibility to MS and the eye velocity induced during an OVAR. More precisely, MS occurrence is positively correlated to the horizontal components of the eye velocity, i.e. the modulation amplitude and the bias. By calculating the vectorial sum of the eye velocities obtained in the three stereotaxic planes (3D eye velocity), we demonstrate the existence of a specific link between the length of 3D eye velocity and MS susceptibility. Thus, the following discussion will focus on the computation by the CNS, of the various interacting sensory signals that might account for MS occurrence.

MS scores and motion sensation

As part of this study, we investigated susceptibility to MS by repeatedly evaluating the intensity of the different symptoms during OVAR, and by comparing these experimental values to the scores obtained by the same subjects on MS susceptibility questionnaires (MSQ and HQ). In contrast to MSQ scores, the HQ scores did not correlate to the MS induced by this experimental otolith stimulation. Accordingly, weak correlations are reported between the responses to the questionnaires HQ and MSQ and the different MS scores obtained during laboratory examination (Golding, 1998; Miller and Graybiel, 1972). A possible reason for this discrepancy is that experimental stimulations constitute acute, standard and objective conditions for MS occurrence, while in contrast, responses to questionnaires rely on the multifactorial nature of MS occurrence, and on the subjective estimation of past experience. Another possible reason can be that MS elicited by OVAR stimulation is quite specific to otolith function while the questionnaire HQ reflects a general MS susceptibility evaluation. As described in previous studies using OVAR (Denise et al., 1988), subjects reported various sensations of complex motion in space, including a body translation along a cylindrical or conical path and cycloid-like trajectories. Rare were the subjects who reported simple movements, like tilted rotation or body swing. Whatever the sensation experienced, no clear link was observed between the type of body motion sensation and susceptibility to MS.

MS genesis and kinematic estimation process

Concerning the relation between MS and oculo-motor responses to vestibular stimulation, no correlation was observed between MS scores and VOR gain during per- and post-rotatory nystagmus, in agreement with Quarck et al. (2000). In contrast to the observations of Quarck et al. (2000), the experimental susceptibility to MS was not directly correlated to the time constant of per- and post-rotatory nystagmus. Nevertheless, a multi-variable analysis showed that susceptibility to MS can be predicted by the combined occurrence of a short time constant of per- and post-rotatory nystagmus (reflecting a short time-constant of the cVOR), and of a large amplitude of the eye velocity (modulation and bias) induced by OVAR (reflecting efficient oVOR).

As we know, the time constant of the VOR reflects the activity of a velocity storage circuit, the so-called VSM, embedded in pathways of the brain stem and cerebellum and controlled by the cerebral cortex, which provides low frequency components of eye velocity during vestibular stimulation (Robinson, 1975, 1977; Waespe and Henn, 1977; Waespe et al., 1983; Raphan et al., 1977, 1979; Angelaki and Hess, 1995; Ventre-Dominey et al., 1999, 2003). Receiving afferent sensory signals from different receptors (visual, vestibular, proprioceptive) as well as efferent copies of eye and head motor signals, the VSM computes simultaneously and iteratively coherent estimates of the kinematic variables of head and eye movements (Hain et al., 1988; Droulez and Darlot, 1990; Angelaki and Hess, 1994, 1995; Tweed et al., 1994; Hess and Angelaki, 1997, 1999; Zupan et al., 2002). The role of the VSM in genesis of MS symptoms has been previously proposed in behavioral studies in humans (DiZio and Lackner, 1991; Quarck et al., 1998, 2000; Bos et al., 2002; Cohen et al., 2003; Dai et al., 2003; Lackner and DiZio, 2006), especially in combined visual- or otolith-canal stimulation provoking dynamic changes of the VSM. During OVAR, the vestibular signal resulting from the activation of the otolith receptors reaches the VSM which computes a head velocity signal sent toward the oculomotor plant. During canal-otolith cross-coupling, such as pitch while rotating, the velocity estimate elicited by canal stimulation is modified due to a shortening of the cVOR time constant driven by the otolith input via the cerebellar uvula and nodula (Angelaki and Hess, 1994; Sheliga et al., 1999; Wearne et al., 1999; Raphan and Cohen, 2002; Bockisch et al., 2003; Cohen et al., 2003; Dai et al., 2003). In our study, we found that MS susceptibility co-occurs with decreasing time constant of the cVOR and increasing OVAR related eye velocity. The interpretation of these results can be twofold: 1) as there was no direct correlation between MS score and VOR time constant, this finding revealed only by multivariate regression analysis might be exclusive to the multiple comparison including otolith velocity parameters and VOR time constant, and alternatively 2) the VSM dynamic measured during a pure canal vestibular stimulation such as the horizontal rotation used in our experiment, does not completely reflect the dynamic of the VSM activity during the OVAR stimulation or during an interactive canal-otolith situation. As we could not check the performance of the VOR after the OVAR stimulation due to the subject discomfort, the implication of the velocity storage process in our MS symptoms during OVAR cannot be fully assessed from our results.

In the current study, we observed a strong correlation between the MS susceptibility and the horizontal eye velocity in response to OVAR, including the modulation related to changes of head position in space. As no relationship was found between MS occurrence and vertical or torsional eye velocities, the discussion will focus on the processing of vestibular signals which induce eye movements in the horizontal stereotaxic plane during OVAR.

Internal 3D velocity representations and susceptibility to MS

When the head is rotated around an off-vertical axis, the CNS processes the otolithic signals and builds central representations of the kinematic variables: head rotational velocity in space, head translational acceleration and velocity in space, together with head orientation with respect to gravity. The resulting slow phase eye velocity in the horizontal stereotaxic plane (X-Y) can be described by two components: 1) a constant velocity, traditionally termed “bias,” compensating for the perceived head rotation velocity, i.e. the central representation of head rotation velocity in space; 2) a sinusoidal modulation compensating for the component (along the Y axis) of a perceived head translational velocity in space. In the current study, we analyzed otolith ocular responses in the low frequency domain (0.16 Hz) which drives the linear vestibulo-ocular responses relevant to head tilt. As mentioned by Paige and Tomko (1991), the linear vestibulo-ocular response results from two frequency-selective processes: a high frequency process for head translation (natural movements) and a low frequency otolith process for head tilt (tilt, OVAR). At low frequency rotation, the horizontal translational velocity component should thus be less robust than at high frequency. In our subjects, we found a clear correlation between MS and modulation of eye velocity in the horizontal plane and less so in the velocity bias. As modulation amplitude increased, so did subject’ susceptibility to MS. Moreover, in the most susceptible subjects the eye velocity was significantly dependent on the head position as compared with less susceptible subjects.

Previous studies reported that an orientation discordance computed in the VSM between gravity and the axis of eye rotation might be a critical factor for MS genesis (Wearne et al., 1999; Sheliga et al., 1999; Raphan and Cohen, 2002; Bockisch et al., 2003; Cohen et al., 2003; Dai et al., 2003, 2007). In order to verify such an orientation discrepancy responsible for MS and to quantify the performance of the central vestibular system, we measured the resultant tridimensional eye velocity vector and its angle to the head axis that reflect the effective direction of the otolith ocular response. While the length of the 3D velocity vector was higher and head position dependent in MS susceptible subjects, the angle to the head axis remained at the same values in the two MS groups with few variations as the head position changed. Consequently, we assume that MS induced during OVAR is linked more to the length of the 3D velocity vector than to the direction of the resulting 3D eye velocity vector.

CONCLUSION

In summary, this study provides further evidence on the link between MS genesis and otolith eye movement mechanisms. Indeed, we demonstrated that the otolith-induced MS susceptibility evaluated by MS growth rate is closely correlated to the eye velocity induced during OVAR independently of the direction of the eye rotation axis in head-centered coordinates.

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