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RESEARCH ARTICLE

Prolonged reduction of motion sickness sensitivity by visual-vestibular interaction

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Abstract The angular vestibulo-ocular reflex (aVOR) and optokinetic nystagmus (OKN) were elicited simultaneously at low frequencies to study effects of habituation of the velocity storage time constant in the vestibular system on motion sickness. Twenty-nine subjects, eleven of whom were susceptible to motion sickness from common transportation, were habituated by sinusoidal rotation at 0.017 Hz at peak velocities from 5 to 20°/s, while they watched a full-field OKN stimulus. The OKN stripes rotated in the same direction and at the same frequency as the subjects, but at a higher velocity. This produced an OKN opposite in direction to the aVOR response. Motion sickness sensitivity was evaluated with off-vertical axis rotation (OVAR) and by the response to transportation before and after 5 days of visual-vestibular habituation. Habituation did not induce motion sickness or change the aVOR gains, but it shortened the vestibular time constants in all subjects. This greatly reduced motion sickness produced by OVAR and sensitivity to common transport in the motion susceptible subjects, which persisted for up to 18 weeks. Two motion susceptible subjects who only had aVOR/OKN habituation without being tested with OVAR also became asymptomatic. Normal subjects who were not habituated had no reduction in either their aVOR time constants or motion sickness sensitivity. The opposing aVOR/OKN stimulation, which has not been studied before, was well tolerated, and for the first time was an effective technique for rapid and prolonged habituation of motion sickness without exposure to drugs or other nauseating habituation stimuli.

Keywords Motion sickness · Habituation/adaptation · Optokinetic nystagmus (OKN) · Vestibulo-ocular reflex (aVOR) · Velocity storage · Off-vertical axis rotation (OVAR) · Nystagmus · Motion susceptible

Introduction

Sensorimotor systems frequently respond to complex spatial modalities with production of motion sickness symptoms, ranging from malaise to dizziness and vomiting. This malady has been recognized since at least the ancient Greeks (Reason and Brand 1975) and is attributable to activation of the autonomic system in response to vestibular stimuli (Yates 1992; Yates et al. 1998; Benson 2002; Dai et al. 2010). While normal individuals may only become sick in harsh force environments, including rough seas (Kennedy et al. 1968) and space flight (Graybiel et al. 1975; Money 1981; Putcha et al. 1999), motion susceptible individuals can readily become sick when travelling by car, bus, train, or plane (Turner and Griffin 1999), which we term 'common transport'. In a study by the United States Navy, motion sickness was encountered in 13.5% of aircrew, with 5.9% of them experiencing vomiting (Hixson et al. 1984). Turner and Griffin (1999) surveyed 3,256 people traveling by bus or coach in the UK; 28.4% reported some level of sickness. Of these, 12.8% had nausea, and 1.7% reported vomiting. Thus, the number of people who are susceptible to common transportation is not negligible.

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The neural mechanisms involving the production of motion sickness have been a matter of conjecture. The vestibular system plays a critical role in the production of motion sickness, and with relatively few exceptions (Johnson et al. 1999), motion sickness either disappears or is ameliorated after loss of vestibular function (Money 1972). Sensory conflict theory (Irwin 1881; Guedry 1970; Reason and Brand 1975) has generally been evoked to explain the origin of motion sickness, but the nature of the conflict is not exactly known. An incongruity between the internal vertical and sensed vertical has been postulated to be the conflict (Oman 1982; Bles 1988), but this postulate has not been tested quantitatively.

We have recently studied the eye movements of subjects who respond to stimuli that provoke motion sickness (Cohen et al. 2003, 2008; Dai et al. 2003, 2007a, 2009, 2010). We demonstrated that motion sickness is triggered by a disparity between the vestibular eye velocity response vector and the orientation vector of velocity storage, which is close to gravity (Dai et al. 1991, 2010; Raphan and Sturm 1991; Raphan and Cohen 2002). The neural structures that mediate the orientation disparity are likely to involve the nodulus and uvula of the vestibulo-cerebellum (Waespe et al. 1985; Wearne et al. 1998; Cohen et al. 2002), since motion sickness disappears or is substantially diminished after surgical ablation of these structures in dogs (Bard 1945; Wang and Chinn 1956). Similarly, humans with cerebellar atrophy involving the nodulus and uvula also have little motion sickness sensitivity (Dai et al. 2007b).

It is known that the motion sickness sensitivity of individuals is associated with the dominant vestibular time constant, i.e., with the time constant of velocity storage. A decrease in the time constant is tightly linked to a reduction in motion sickness sensitivity (Clément et al. 2001; Dai et al. 2003, 2007a, 2010; Cohen et al. 2008). This finding is also in line with the general knowledge that people with a longer vestibular time constant are more prone to motion sickness (Hoffer et al. 2003) and that the reduction in the time constant by baclofen (Cohen et al. 1987; Dai et al. 2006) reduces motion sickness sensitivity (Cohen et al. 2008). Thus, it is likely that motion sickness sensitivity is related to the magnitude of the velocity storage time constant and further, that a reduction in the time constant can reduce the contribution of velocity storage to motion sickness.

A number of studies have attempted non-pharmacological approaches to reduce the time constant. These include low-frequency oscillations in darkness (Blair and Gavin 1979; Jäger and Henn 1981) and repeated constant velocity step rotations (Cohen et al. 1992; Clement et al. 2008). These methods of habituation have used rotational velocities of about 60°/s with long durations of training. In this study, we used a new approach, in which opposing visual and vestibular stimuli at low stimulus velocities (5–20°/s) and a low frequency (0.017 Hz) were used for habituation, a stimulus that was non-stressful, fast, effective, and long lasting.

Methods

Subjects

Twenty-nine subjects (ages 25–45) participated in this study. Eleven motion susceptible subjects were selected according to their history. The prime criterion was the occurrence of motion sickness when travelling in common transport, i.e., by car, bus, train, or plane. There was a heavy gender bias. Ten of the susceptible subjects were female. Eighteen subjects who were not susceptible to common transport formed a control group (9 males and 9 females). All subjects had no known history of vestibular or auditory dysfunction, migraine headaches, anxiety disorder, claustrophobia, seizures, severe vasovagal reactions or cardiovascular or autonomic disease. None had previously been tested for motion sickness susceptibility. Subjects with infrequent and mild motion sickness during common transport were excluded, as were those who were sick only when reading during rides, or who were uncomfortable or sick only occasionally.

During the subject selection process, they were taught to rate their motion sickness on a scale of 0–20 (see the Sect. Motion sickness evaluation for the derivation of the motion sickness rating). A measure of the severity of motion sickness was obtained by taking the average subjective scores of motion sickness during episodes of transportation in the last 1–2 years, divided by the number of trips during this period. For example, if a subject made two recent trips by car and reported severe motion sickness with a score of 20 (vomiting) on one occasion during a long distance trip, and a score of 12 (nauseated) during a short trip, we rated the average motion sickness score as 16. Although admittedly arbitrary, this gave us a baseline motion sickness score before habituation. After habituation, motion sickness induced by common transport was rated in a similar fashion at the end of the 1st, 4th, and 18th week. Five susceptible subjects were followed for 10 months.

The normal subjects (ages 21–32, 9 males and 9 females) were divided evenly into two groups: Normal Groups 1 and 2 (Nl-Group 1 and 2). Nl-Group 1 was tested with OVAR and then habituated using visual-vestibular interaction. Nl-Group 2 was only tested with OVAR to determine whether the OVAR testing, which was performed once a week, had also habituated their motion sickness susceptibility. Motion susceptible subjects were also divided into two groups: MSS-Group 1 (9 subjects) received both the OVAR tests and the habituation training

and MSS-Group 2 (2 subjects) only had habituation training. The second subgroup always vomited after riding for several hundred meters, and we considered them as incapable of taking the OVAR testing. This determined whether OVAR had influenced the effects of habituation in the motion sickness susceptible subjects.

After agreeing to participate, they signed an Informed Consent Form approved by the Institutional Review Board of the Mount Sinai School of Medicine, New York.

Equipment and eye recordings

Experiments were conducted using a rotating chair enclosed in a circular room of 2 m diameter. An OKN stimulator on the ceiling projected rotating black and white stripes on the wall that elicited optokinetic nystagmus and optokinetic after-nystagmus (OKN and OKAN). The black and white stripes were evenly spaced and subtended a visual angle of 5°. The rotating chair was capable of accelerations of 200°/s^2. The room and chair could be tilted together hydraulically up to 30° to provide off-vertical axis rotation (OVAR). Subjects were seated in a chair with a seat belt and a soft head band that immobilized the body and head throughout the habituation.

Horizontal and vertical positions of the right eye were recorded by video-oculography (ISCAN) at 60 fr/s with an accuracy of >0.5° over ±30°. Eye position was calibrated while subjects watched a laser dot displayed in front of them and at angles of ±15° horizontally and 15° upward. Eye positions and slow phase eye velocities were positive for eye movements to the left and down from the subject's perspective. Eye movements were recorded during the baseline aVOR testing and at the beginning of later test sessions to check for aVOR gains and time constants. Eye movements were generally not recorded for every individual during each OVAR session or during aVOR/OKN habituation.

Baseline aVOR testing

Subjects were tested before each OVAR session with two per-rotatory and two post-rotatory steps at velocity of 60°/s (acc. 200°/s^2) in darkness (Dai et al. 2010). Subjects were not tested after OVAR, because any motion sickness that had been generated during OVAR would affect the induced responses. Per- and post-rotatory steps were also given before and after each habituation session.

OVAR testing

A complete description of OVAR testing has been given elsewhere (Dai et al. 2010). Briefly, subjects were initially rotated at 60°/s to the right in darkness while upright. After the per-rotatory nystagmus had disappeared, the chair was tilted 20° from the vertical over 15 s while the chair and subject continued to rotate. This induced nystagmus after about a 1-s delay and motion sickness. After a subject reported a motion sickness score of 20, or after 15 min of exposure to OVAR, the test was stopped by tilting the chair back to the vertical. Thus, for example, subjects could have a maximum of 150 rotations at a rotational velocity of 60°/s if they completed the entire OVAR test without overwhelming nausea.

Data analysis

Horizontal positions from the ISCAN system were filtered with analog filters from DC to 20 Hz before being resampled at 600 Hz/channel. Eye position data were digitally differentiated to obtain eye velocity. Quick phases were removed, leaving slow phase eye velocity for analysis. 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 (Dai et al. 1999). The gain and time constant were averaged from the two per- and two post-rotatory tests. One-way repeated measures ANOVA and Student's t test were used for all data analyses. In addition, post hoc power analysis was also used to determine the effect of habituation on motion sickness from common transport.

Motion sickness evaluation

During the subject selection period and before the experiment, subjects were trained to report motion sickness scores with a simplified Pensacola scale from 0 to 20 (Hecht et al. 2001; Young et al. 2001; Dai et al. 2003, 2010). Zero was no reaction, 5 was starting to feel warm or have slight malaise, 10 was moderate gastro-intestinal distress and/or dizziness with or without sweating, 15 was a strong feeling of nausea or dizziness, but the test could still be continued, and 20 was the end point at which time, the subjects felt that they could go no further. This could be due to a sense of imminent emesis or a strong sense of dizziness. Subjects were in continuous communication with the experimenters during the test. The score of motion sickness was reported verbally every 5–10 s, depending on the pace of development of motion sickness. We considered that the score associated with the symptoms represented the magnitude of motion sickness. For example, if a subject was aware of a 'stomach reaction', she/he was instructed to report a score of 10. During the subject selection, they had to provide their symptoms and their scores during transportation. During OVAR, the investigators also asked about the symptoms to confirm the score,

especially during the first OVAR test. For inter-individual comparisons, an index of motion sickness sensitivity (MSS) was used, which was the ratio between the final score and number of revolutions of OVAR that subjects had completed. This normalized metric, which had units of score per head turn, made comparisons between subjects possible. More susceptible subjects had a higher value of MSS and vice versa. The scoring system was also used to scale the intensity of motion sickness encountered during transport in the follow-up.

Experimental design of habituation

The basic hypothesis was that the velocity storage time constant would be reduced by generating out-of-phase, low-frequency optokinetic and vestibular stimuli, which are the two major inputs to velocity storage from the visual and vestibular systems. The frequency had to be low, so as to be appropriate for activating the response characteristics of velocity storage, and not to overwhelm the motion susceptible subjects with nausea. Based on the vestibular neuron recordings (Boyle et al. 1985; Yakushin et al. 2006), in which there is no phase shift for OKN stimuli of less than 0.05 Hz, we assumed that there was no phase shift of the central OKN response. Thus, the OKN stimulus velocity was set to synchronize with the aVOR response so that they were180° out-of-phase.

To produce an OKN stimulus that was 180° out-of-phase with the aVOR, the OKN stimulus had the following function:

$$A\sin(2\pi ft) + B\sin(2\pi ft + \phi) \quad (1)$$

where A is the amplitude of the chair velocity, and B is the amplitude of the aVOR response; f is the frequency (0.017 Hz), and ϕ is the phase advance of the aVOR with respect to the chair velocity. Function (1) can be simplified as:

$$C\sin(2\pi ft + \phi) \quad (2)$$

where C is the amplitude of OKN, and ϕ is the phase of OKN with respect to the chair velocity. Function (2) was used to drive the OKN stimulator.

Experimental protocol

A schematic diagram of the protocol is shown in Fig. 1. OVAR was given on Day1 (OVAR1), Day 8 (OVAR2), Day 22 (OVAR3), and Day 29 (OVAR4). OVAR testing at one-week intervals does not change aVOR gains or time constants (Dai et al. 2010). Five consecutive days of habituation were performed between OVAR 2 and 3, from Day15 to 19. Each subject was habituated for 40 min/day, with a rest of 5 min in between. The subjects were allowed to listen to music on their mobile devices during the habituation.

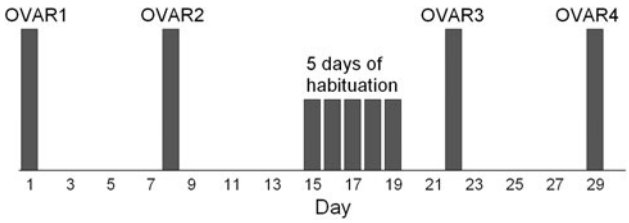

Fig. 1 Schematic representation of the experimental protocol. Subjects received the first OVAR test (OVAR 1) at the start of the experiment. One week later, they had a second OVAR test (OVAR 2). In the third week, they received 5 days of OKN/aVOR habituation. They were then tested again with OVAR in the third (OVAR 3) and fourth weeks (OVAR 4)

Determination of the maximum stimulus velocity and phase for habituation

It has been demonstrated previously that the post-rotatory aVOR can be reduced by an oppositely directed OKAN (Jung 1948; Cohen 1974; Raphan et al. 1979; Cohen et al. 1981). We first determined the largest aVOR response in our subjects that could be cancelled by OKAN. This information allowed us to use rotational velocities that produced matched aVOR and OKN responses. Four subjects were rotated in light at three rotational velocities, 20, 40, and 60°/s, while they watched a spatially stationary background composed of 5°, black and white stripes. The stimulus induced both per-rotatory nystagmus and OKN. After 2 min, the chair was stopped and the lights were extinguished, inducing post-rotatory nystagmus with contralateral slow phase velocity and OKAN with oppositely directed slow phase velocity.

Among the three rotational velocities, only rotation at 20°/s produced complete post-rotatory cancellation (Fig 2). The post-rotatory aVOR had a time constant of 12.4 s with an initial eye velocity of 12.4°/s (Fig 2a), while the OKAN had a time constant of 11.2 s with an initial velocity of −13.6°/s (Fig 2b). There was little or no eye velocity after the stop in darkness (Fig 2c). From this, we determined that the maximum effective stimulus velocity to produce precise cancellation between the vestibular and the visual inputs would be 20°/s or less. This value was in line with the maximum OKAN value that can be produced in human (Cohen et al. 1981; Jell et al. 1984; Fletcher et al. 1990).

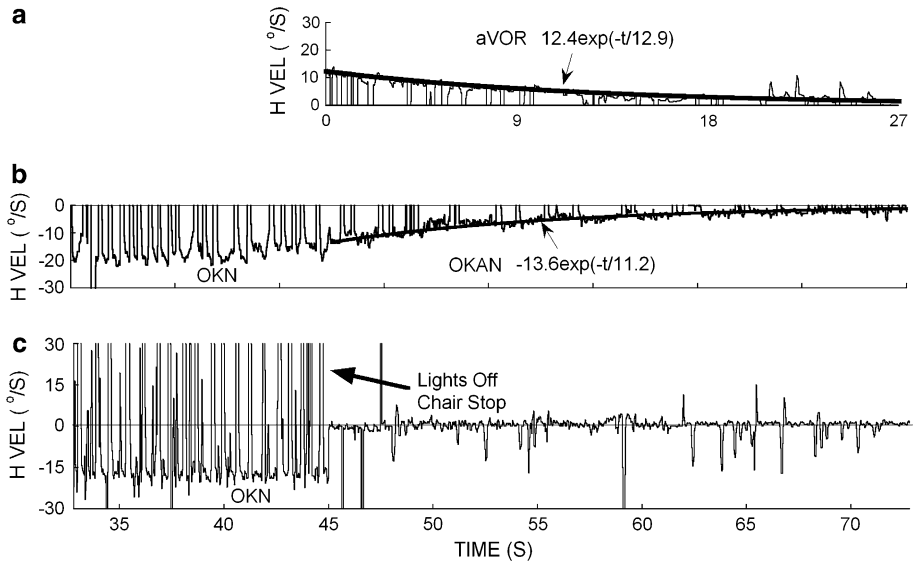

Fig. 2 Cancellation of the post-rotatory aVOR response by OKN. **a** Post-rotatory aVOR in response to 20°/s rotational velocity. **b** OKN and OKAN from stimulation at 20°/s. **c** Rotation in light at 20°/s with a stop in darkness. Note the cancellation of the post-rotatory aVOR by the OKAN after Lights Off/Chair Stop in **c**

The habituation paradigm is depicted in Fig 3a. As in the experiments of Jäger and Henn (1981), there was a phase advance of the aVOR of 31.9 ± 3.1° with a gain of 0.68 ± 0.29 in four normal subjects during oscillation at 0.017 Hz with a peak rotational velocity of 20°/s (Fig. 3b). Note that the OKN velocity and the aVOR response were 180° out-of-phase (Fig 3c, blue and black traces).

Some motion sickness was produced in the first habituation for susceptible subjects when they were rotated at 15 or 20°/s. Because of this, subjects were first habituated by rotation at 10°/s. If they had dizziness and/or malaise at this rotational velocity, it was reduced to 5°/s. No dizziness was reported in response to this velocity. Following rotation at the lowest velocity, it was possible to raise the rotational velocities gradually to 20°/s, day by day, without causing discomfort.

Effects of habituation:

All of the normal and susceptible subjects completed the study. The normal subjects had no symptoms of motion sickness when being habituated at velocities of 10°/s for the first time. In contrast, only one susceptible subject did not have motion sickness symptoms at this stimulus velocity; the others were rotated at 5°/s after experiencing minor motion sickness 5–20 min later. No subjects complained of motion sickness, when experiencing 5°/s over the oscillation period of 40 min.

Before habituation, the time constants of susceptible subjects were longer than those of the normal subjects (18.3 ± 2.4 s, $N = 11$ vs. 15.5 ± 2.7, $N = 18$; $P = 0.007$, unpaired with unequal variance). The time constants were progressively reduced by habituation in both normal ($P < 0.0001$, $df = 89$, $F = 11.8$) and susceptible subjects ($P < 0.0001$, $df = 109$, $F = 7.9$). Immediately after the first habituation session, the time constants declined by 32% to 12.5 ± 2.0 s in susceptible subjects and by 21% to 12.8 ± 3.8 s in normal subjects. Thus, their time constants were at the same level by the end of the series (11.1 s; $P = 0.9$). The reduction in the time constant was not maintained as well between sessions by the normal (Fig. 4a) as by the motion susceptible subjects (Fig. 4b).

There was no change in the aVOR gains for either normal (Fig. 4c) or susceptible subjects (Fig. 4d) over the habituation period. When the first and last OVAR test in the two normal groups were compared (Fig. 5), there was also no difference in the aVOR gains. Thus, neither the low-frequency, low-magnitude vestibular and visual stimuli that had primarily affected velocity storage, nor OVAR had altered the aVOR gains, which are produced by the rapid component of the aVOR response (Raphan and Cohen, 2002 for review). Of interest, the aVOR gains were higher in the nine susceptible subjects than the 18 normal subjects (Fig. 5), raising the interesting question of whether the motion sickness susceptible subjects were receiving more vestibular input from the semicircular canals when they moved their heads than the non-susceptible subjects.

The aVOR time constants were determined at the onset of each session, before the subjects were tested with OVAR. Both the normal and motion sickness subjects (Fig. 6a, b) had no significant change in their time constants at the beginning of the first two OVAR sessions. Their time constants became significantly shorter, however, when they were tested at the beginning of the third session (Fig. 6a, b), a result of the habituation between the 2nd and 3rd OVAR tests. A change in time constant was not present in normal subjects who had not been habituated

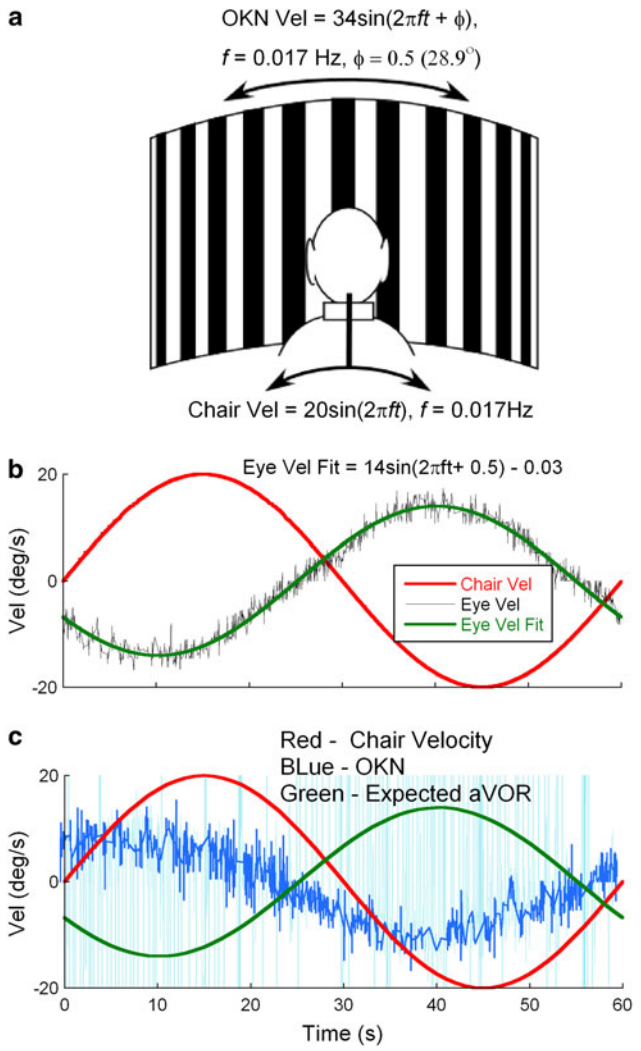

Fig. 3 **a** Experimental setup for the cancellation of the aVOR with OKN. The chair and OKN drum were oscillated concentrically at a frequency (*f*) of 0.017 Hz. The OKN had a phase lead to chair rotation of ϕ degrees. **b** aVOR response showing a phase advance. The aVOR slow phase eye velocities were fit with a sine function (*green line*) that had an amplitude of 14°/s and a phase advance of 0.5 radians (28.6°). **c** Visual-vestibular interaction. The expected aVOR (*green line*) was opposed by the OKN (*blue line*)

(Fig. 6c), demonstrating that it was the habituation, not the OVAR testing that had shortened the aVOR time constants.

OVAR tests of motion sickness sensitivity

OVAR, which was used to test motion sickness sensitivity (MSS) is a well-understood technique, which produces its effects through the otolith organs and activation of velocity storage (Dai et al. 2010). On average, the MSS scores of the motion sickness susceptible group derived from the OVAR testing before habituation were higher than those of the normal subjects (Fig. 6d, e, 1st and 2nd tests; $P = 0.04$, $N = 9$, unpaired). After habituation, this difference disappeared and the MSS were approximately the same in the 3rd and 4th OVAR tests ($P = 0.99$).

There was a smaller reduction in MSS in the normal group between the 2nd and the 3rd OVAR tests (Fig. 6e), but a striking reduction in the sensitivity of the motion sickness susceptible group to OVAR over the same period (Fig. 6f). The reduction in motion sickness sensitivity in both the normal and the motion sickness susceptible groups closely paralleled the reduction in their time constants (Fig. 6a, b). The group of normals that did not receive habituation had no changes in their aVOR time constants (Fig. 6c) or in their motion sickness sensitivities (Fig. 6g). These data indicate that the higher MSS in susceptible subjects was reduced to the level of normal subjects after five habituation sessions.

Motion sickness during 'Common Transport'

Subjects were trained to report motion sickness scores with a simplified Pensacola scale at the first session, before starting habituation. At that time, they gave an evaluation of the motion sickness they had experienced recently on common transport, using the same scale as utilized in OVAR test sessions and put a score from 1 to 20 on each experience. The scores were then averaged to obtain their motion sickness sensitivity to 'common transport'. Similar numerical values were assigned to their motion sickness sensitivity after they had gone through the habituation process.

Motion sickness had completely disappeared in 10 out of the 11 subjects one week after the completion of the last OVAR test or 2 weeks after the habituation was completed (Fig. 7). This included the two subjects who only had had habituation and no OVAR testing. Before the habituation, the average score of motion sickness in common transport for these 11 motion susceptible subjects was 13.0 ± 4.4. After habituation, it was reduced to 1.5 ± 3.1 eighteen weeks later, which was a significant difference ($P = 0.001$, $N = 11$; Paired Student's *t* test) with a power of 100%. For example, one subject who could not ride on a city bus for two blocks (about 0.2 miles) without experiencing severe motion sickness became asymptomatic, and she was able to ride for 50 min on a bus afterward without difficulty. She also was able to forego taking an anti-motion sickness drug (diphenhydramine) before each bus ride, as she usually did. Another subject who had previously always vomited during air travel was able to fly without becoming motion sick on two separate occasions 2 months apart after habituation. There was some loss of the habituation in three subjects four and one-half months after habituation, but they reported that the severity of motion sickness was significantly reduced, relative to what they had experienced before. These three subjects rated their scores at 3, 4, and

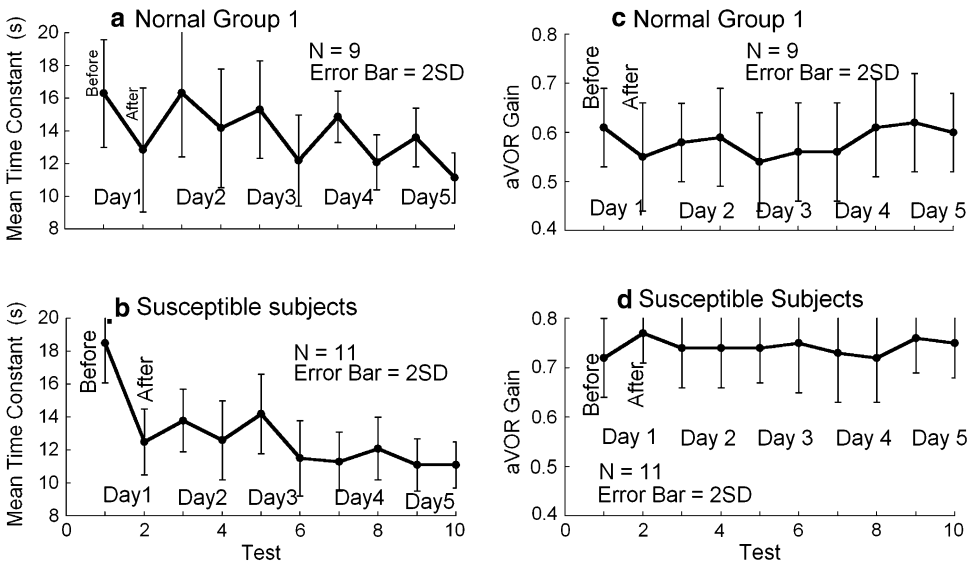

Fig. 4 Horizontal aVOR time constants (**a**, **b**) and gains (**c**, **d**) before and after each day of habituation over 5 days. The *vertical bars* show ± 1 SD. **a** There was a reduction in time constant at the end of each day of habituation in the normal group that returned to a lower level on the following day. **b** The susceptible subjects had a large initial fall in time constant that was further reduced during the week. **c**, **d** The aVOR gains were unaffected by the habituation. The gains were higher in the susceptible subjects ($P = 0.007$, unpaired Student's t test)

10 out of 20. The other eight subjects were still free of motion sickness sensations during common transport four and a half months later (Fig. 7).

Five patients returned after 10 months, and their aVOR time constants and motion sickness scores from common transport were tallied (Table 1). Their time constants were 18 ± 1.9 s before habituation, 10 ± 1.5 s just after habituation, and 14.2 ± 2.5 s 10 months later. In three of the subjects (S's 1, 2, 4), the time constants were somewhat longer than just after habituation, and in two (S's 3, 5), the time constants were close to their original value before habituation. Motion sickness scores were all less than when they entered the study, 5.2 ± 4.8 vs. 17 ± 3.1. Thus, there was some return toward the pre-test values of the time constants, and a slight increase in motion sickness scores when compared to the values 1 week after habituation. All of the five subjects, however, were better able to travel in common transport, and motion sickness appeared only when they had been subjected to long rides or strong turbulence in aircraft.

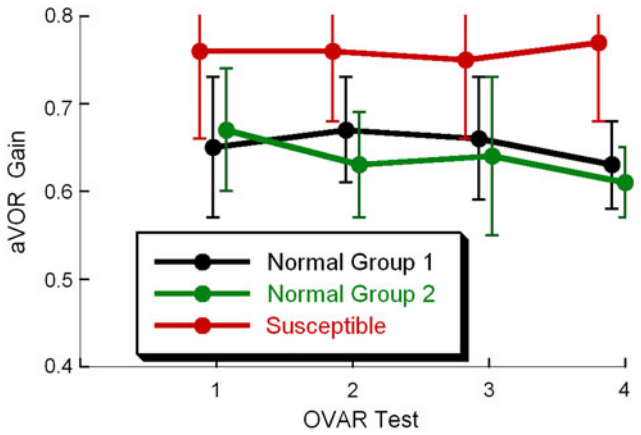

Fig. 5 Mean aVOR gains of normal and susceptible subjects over the test period. The gains of the susceptible subjects (*red line*) were greater than those of the normal subjects ($P = 0.007$, unpaired Student's t test). The *error bars* (±1 SD) are shifted to the *right* or *left* to avoid overlap

Discussion

In this study, we have demonstrated a technique to habituate the time constant of velocity storage, which was effective in reducing motion sickness evoked by common transportation for prolonged periods. The motion sickness sensitivity of the susceptible individuals, which was significantly higher before habituation, was reduced to the same level as that of the normal subjects (Fig 7). The effect of habituation to travel in common transport lasted at least 18 weeks and was present in 5 subjects 10 months later (Table 1). The reduction in motion sickness sensitivity was unrelated to testing with OVAR since the susceptible subjects who only had the habituation also became resistance to common transportation that had made them sick before. Moreover, normal subjects who had the OVAR test alone did not show the same effects of habituation on motion sickness, although we could not rule out the 'placebo effect' since they did not spend times in the laboratory during the habituation period.

The habituation that canceled the low-frequency aVOR with OKN was rapid and produced no significant side effects in the motion susceptible subjects. Therefore, it appears to have great potential for use in reducing the motion sickness sensitivity of these subjects.

Stimulation by actively pitching or rolling the head while rotating around a vertical axis is a potent stimulus for producing strong motion sickness (Purkinje 1820; Miller and Graybiel 1973; Guedry et al. 1998; Young 1999;

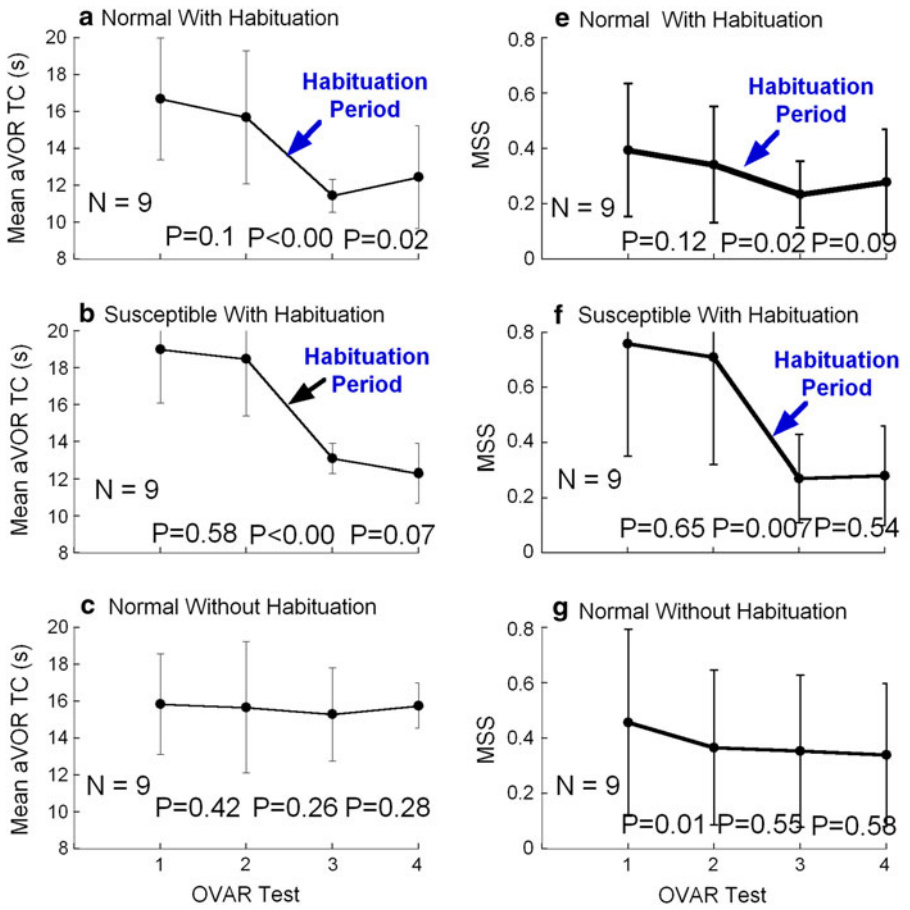

Fig. 6 Change in aVOR time constants and motion sickness sensitivity (MSS) as a function of OVAR tests, as well as the effect of habituation on the time constant and MSS for normal subjects (**a**, **e**), susceptible subjects (**b**, **f**), and normal subjects without habituation (**c**, **g**). No change in time constant of the aVOR was produced by OVAR (**c**). Changes only occurred if there was a period of habituation (**a**, **b**). Concurrently, there was a reduction in MSS after habituation (**e**, **f**). The *vertical bars* show ± 1 SD

Clément et al. 2001; Dai et al. 2003), and it has also been widely used to study habituation of motion sickness (Guedry and Graybiel 1962; Guedry and Benson 1978; Lackner and Graybiel 1980; Bles et al. 1998; Clément et al. 2001). After repetitive exposure, most individuals adapt to this stimulus and their motion sickness abates (Guedry et al. 1964; Lackner and Graybiel 1994; Young et al. 2001; Dai et al. 2003). Head movement rotated on the torso is nauseating and also was used to habituate motion sickness sensitivity (Rine et al. 1999). All of these various stimuli are stressful, especially for people with heightened motion sickness susceptibility. Our approach was different in that we used stimulus of low magnitude and low frequency that did not cause motion sickness during the habituation.

We have previously shown that a reduction in motion sickness sensitivity is reciprocally coupled to a reduction in velocity storage time constants (Dai et al. 2003). Susceptible subjects who only had the habituation and were not tested with OVAR also became resistance to situations that produced motion sickness. This emphasizes the importance of the reduction in time constant of the aVOR for reduction of motion sickness sensitivity.

Vertical linear acceleration is also a potent stimulus for motion sickness, and a moving vehicle can produce both

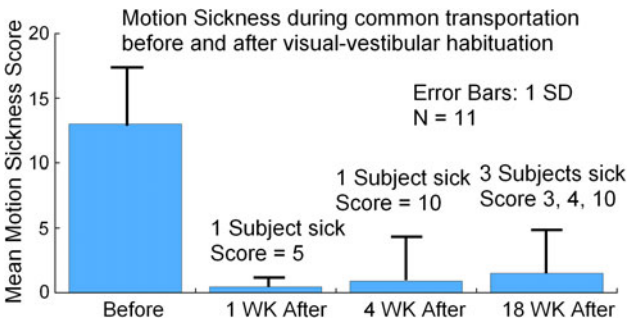

Fig. 7 Average motion sickness scores during transportation before and after habituation. There was a significant reduction in motion sickness among motion susceptible subjects that persisted for 4 weeks in 10 subjects, and for 18 weeks in 8 of the 11 subjects

angular and linear accelerations. Thus, some or most of the sensitivity to riding in common transport could have been due to motion sickness evoked by low-frequency vertical and horizontal linear motions. How linear acceleration might impact velocity storage is not known. (Turner and Griffin 1999). Regardless of whether it was the linear or angular stimuli or a mixture of both that had evoked the motion sickness, alteration of the velocity storage time constant was effective in reducing the motion sickness

Table 1 Ten-month follow-up of 5 motion sickness susceptible subjects with motion sickness scores and aVOR time constants

Subject	Transport	Before		1 week after		10 months after	
		TC (s)	Score	TC (s)	Score	TC (s)	Score
1(R)	Car, Bus	16	12	8.5	0	11	0
2(N)	Car, Bus	18	18	10	0	14	8 (long, rough ride)
3(J)	Car	18	15	9.8	5	17	10 (long ride)
4(C1)	Car, Bus	21	18	12	0	12	8 (long ride)
5(C2)	Air, Bus	17	20	12	0	16	0 (15 in heavy flight turbulence)
Mean		18 ± 1.9	17 ± 3.1	10 ± 1.5	1 ± 2.2	14 ± 2.5	5.2 ± 4.8

1 (R)—TC went from 16 to 8.5 s = 11 s, Time constant remained low. There was no change in her motion sickness susceptibility, even after a recent 3-h ride

2 (M)—TC went from 18 s to 10–14 s, She is still moderately sick after long, rough rides

3 (J)—TC went from 18 to 9.8 s, then 17 s, She scored 10 one month after habituation. Long drives continued to male her sick, but not like before. Car racing now does not caused motion sickness

4 (C1)—TC went from 21 to 12 s and she was not sick after an 8-h ride. Previously, retched after long rides, but no longer

5 (C2)—TC went from 17 to 12–16 s. She previously vomited with each long plane ride. She was not sick on long flights after habituation, except when there was extreme turbulence

susceptibility. This supports our hypothesis that motion sickness is mediated through velocity storage.

Some anecdotal evidence suggests that the habituation effect may have taken place very early in the procedure. One subject noticed that she was no longer sensitive to riding on an escalator after two sessions of habituations. Another subject could enjoy a bus ride for the first time after the second day of habituation. This was coincident with a rapid decline in time constants after the first habituation session. Further habituation in the following sessions progressively reduced the aVOR time constant, but the pace and extent of reduction was slower and smaller. The absolute value of the time constant on average after 5 days of habituation was about 11 s, which is the same (11 s) as that found in subjects who were habituated with roll-while-rotating (Dai et al. 2003).

In this study, the aVOR/OKN stimulation was not specifically set for each individual, and we used an average phase shift and gain of the aVOR for all subjects. Since the phase shift of the low-frequency aVOR response varies individually, particularly when the aVOR time constant becomes shorter, it is possible that the results could have been even better if the phase shift between the optokinetic and vestibular stimuli were specific for each subject at each level of habituation. It would also be useful to match the gender of the motion sickness susceptible and normal subjects, since the control group had males and females in equal number, while the motion sickness susceptible group was heavily skewed toward females. We have demonstrated that the low-frequency stimulus that shortening the dominant time constant played a key role for reducing the motion sickness during common transport. Whether or not the visual OKN stimulus played an additional role was not comparatively studied. This required further study in the future.

The aVOR gains were higher in the motion sickness susceptible subjects than in the normal subjects. This may indicate that they were responding to the increased input from the semicircular canals. A high aVOR gain does not necessarily denote a higher level of motion sickness sensitivity; however, high aVOR gains have been found among professional pilots (Schwarz and Henn 1989; Lee et al. 2004). Figure skaters have a lower gain (Tanguy et al. 2008), and both groups are not motion susceptible (Aschan 1954; McCabe 1960). Perhaps, when a high aVOR gain is linked to a long aVOR time constant, enhanced susceptibility may occur.

There are still a number of unanswered questions. We only studied the larger group of subjects for 18 weeks so that it is unknown for how long the habituation persisted. However, the effects of habituation of motion sickness sensitivity largely persisted in five subjects for 10 months. Further studies on the relationship of the habituation of the velocity storage time constant and the habituation of motion sickness could shed further light on the underlying relationship between the vestibular and the autonomic systems. Whether the reduction in motion sickness sensitivity was only due to habituation of velocity storage, was also due to a reduction in sensitivity of other integrators in the autonomic system that are involved in the production of motion sickness (Benson 2002; Dai et al. 2010) is also unknown. Regardless, our findings show that low-frequency OKN/vestibular interaction, which reduces the time constant of velocity storage, is a potent countermeasure for motion sickness in highly susceptible individuals.

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