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The effects of meclizine on motion sickness revisited

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Aims: Antihistamines make up the first line of treatments against motion-sickness. Still, their efficacy and specific mechanism have come into question. The aim of this study was to investigate the effect of meclizine on motion-sensitivity.

Methods: This study was carried out as a triple-blinded randomized trial involving 12 healthy subjects who were exposed to (i) vestibular (VES), (ii) visual (VIS) and (iii) visual–vestibular (VIS+VES) stimulations in the roll plane. Subjects were divided into 2 groups by stratified randomization, receiving either meclizine or a placebo. Stimulations were carried out before, and after, drug administration, presented at 2 intensity levels of 14 and $28°/s^2$. Eye movements were tracked, and torsional slow-phase velocities, amplitudes and nystagmus beats were retrieved. Subjects initially graded for their motion-sickness susceptibility.

Results: Susceptibility had no effect on intervention outcome. Despite large variations, repeated ANOVAS showed that meclizine led to a relative increase in torsional velocity compared to placebo during vestibular stimulation for both intensities: 2.36 (7.65) from −0.01 (4.17) during low intensities, and 2.61 (6.67) from −3.49 (4.76) during high. The visual–vestibular stimuli yielded a decrease during low acceleration, −0.40 (3.87) from 3.75 (5.62), but increased during high, 3.88 (6.51) from −3.88 (8.55).

Conclusions: Meclizine had an inhibitory effect on eye movement reflexes for low accelerations during VIS+VES trials. This indicates that meclizine may not primarily work through sensory-specific mechanisms, but rather on a more central level. Practically, meclizine shows promise in targeting motion-sickness evoked by everyday activities, but its use may be counterproductive in high-acceleration environments.

KEYWORDS
neuroscience < neuropharmacology, ophthalmology, therapeutics < clinical pharmacology

1 | INTRODUCTION

Motion sickness remains a prevalent reminder of the complexity of our balance system. The sensation is generally thought to be due to a sensory mismatch between vestibular, visual and proprioceptive sensory input.[1] This reaction is considered largely physiological; a sign of our brain receiving conflicting signals on our own postural position in relation to a moving external world.[1,2] While a minor inconvenience to some, others experience more severe symptoms, affecting their everyday life.[3,4]

Medical treatments can generally be divided into 3 groups: antimuscarinic, sympathomimetics and antihistamines.[5] Antihistamines

The authors confirm that the Principal Investigator for this paper is Tony Pansell

make up the first line of treatment for many people, being readily available as over-the-counter medication around the world. In addition, antihistamines are faster-acting and associated with few side-effects.[6] Several studies have been performed on the physiological effects of antihistamines on motion sickness, yielding incongruent results[7-9]; some studies have indicated a strong effect on the vestibular system, whereas others only parts of it, or even no effect at all.[10-13]

Meclizine, 1 of the most available prescription-free motion-sickness pills, is an antihistaminergic H1-antagonist. The drug is described as having good effect against motion-sickness through vestibular modulation, even though the efficacy of this mechanism has come into question.[14,15] The drug is to be used as motion-sickness prevention, reaching its full effect 2 hours after ingestion.[16]

The subjective improvement of motion-sickness medication may be assessed through forms and questionnaires.[17,18] An objective measure of motion sickness is not available at the moment. However, the effect of motion-sickness medications on the vestibular system is heavily implied in its sensitivity to motion detection. In particular, eye-movement analysis, available on both clinical and experimental levels, makes it possible to assess vestibular activity through the oculomotor reflex and its integration with the visuomotor pathways, especially the optokinetic system.[6,9] The 2 systems are deeply integrated to ensure an optimal gaze stabilization during motion under visual flow stimulation, sharing cortical, cerebellar, and brainstem areas.[19-21]

The basis for this objective assessment lies in the vestibulo-ocular reflex (VOR). The VOR, which causes the eyes to adjust in accordance to a vestibular activation, ensures a very effective gaze stabilization on a target during head movements.[22] One function of the VOR is ocular counter-rolling (OCR); the OCR is purposed to counteract a head tilt, stabilizing the eyes in relation to the horizontal reference by the activation of conjugated rotations of both eyes in order to maintain the fusional range and avoid diplopia.[23] The OCR is a vestibular evoked reaction connected to the otolithic and semicircular activity, with the initial phasic component attributed to the semicircular canals (SCCs), while a sustained static position, i.e. changes in amplitude, reflects a utricular activation.[24,25] Therefore, through evaluation of the combined dynamic and static components of an OCR, it is possible to deduce the pattern of vestibular activation.

Ocular torsion can also be triggered by visual rotational stimuli similar to an OCR reaction, albeit to a lesser extent.[26] Torsional velocity also been positively correlated to poorer postural control and increased sympathetic signalling.[27] Consequently, the visual and vestibular systems share a common motor output in response to a central integration of visual–vestibular stimulations. Considering the strong influence of visual–vestibular signalling on motion-sickness triggering, the study of the sensory specific effects of meclizine on eye motility is considered relevant, providing a better insight on the pharmacological mechanism of motion-sickness attenuation under H1 medication. One expression of visuomotor-system activation by visual motion is the optokinetic nystagmus (OKN). The OKN can be deeply affected by central disorders.[28] This highlights the functional range of OKN system and the role of

What is already known about this subject
- Meclizine has a positive subjective effect on decreasing motion-sickness
- The objective measures of meclizine on visual and vestibular systems have yielded very different results, from inhibition to excitation.

What this study adds
- Meclizine has an excitatory effect on the vestibular system compared to placebo.
- Meclizine has an inhibitory effect under normal visual–vestibular conditions, but excitatory during high accelerations.

central modulation. We consider the OKN another relevant parameter to be taken in account for the study of motion-sickness and its pharmacological modulation.

The aim of this study was to identify the effects of meclizine on utricular and semi-circular vestibular function, by evaluating the torsional eye response to movement in the roll plane. This was achieved through rotational stimulation by full-body manipulation and the presentation of visual optokinetic motion, presenting isolated as well as combined visual and vestibular balance provocations.

2 | MATERIALS AND METHODS

2.1 | Subjects

The study involved 12 healthy subjects (6 male, 6 female; mean age 25 years [range 23–34]) with no history of balance problems. Subjects were recruited through friends and colleagues of researchers and participants. All participants received an eye examination to ensure normal corrected visual acuity (≥1.0) stereoscopic vision (Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek test ≥60″), normal eye motility and no latent strabismus larger than 2 exo- or esophoria at distance. All subjects showed normal performance at Romberg test and head impulse test, excluding clinically evident affections of the vestibular system. Subjects' motion sensitivity was graded with the freely available motion sickness susceptibility questionnaire (MSSQ). A score exceeding 11.3 was taken as indicator of an above-average motion sickness susceptibility.[29] The investigation was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects in written form after having been informed of the nature and possible consequences of the investigation. The study was approved by the Regional Ethics Committee of Stockholm (EPN 2018–1768-31-1).

2.2 | Intervention

This study was carried out as a triple-blinded, randomized controlled trial. Subjects were allocated into 2 groups through stratified randomization, 1 receiving meclizine and the other a placebo pill. This randomization was performed using a digital randomization algorithm. A controller with no active involvement in the trials put the 2 different medications in separate opaque plastic medical jars. Both placebo and meclizine were white, round and film-coated. The meclizine was scored and had a diameter of 7.1 mm whilst the placebo was not scored and had a diameter of 6 mm. The placebo consisted of magnesium stearate, povidone and anhydrous lactose. The coating consisted of partially hydrolysed polyvinyl alcohol, titanium dioxide, macrogol 3350 and talc. The test subject was asked to swallow the tablet without looking at it. The key to the randomization was handed over to the test leader after all analysis were completed.

2.3 | Method

All subjects were exposed to 3 distinct protocols, referred to as sensory modalities, allowing for eye movement comparison to visual and vestibular roll stimulations of comparable magnitudes: *visual* (VIS), *vestibular* (VES) and *visual–vestibular* (VIS+VES; Figure 1). Participants were seated in a motorized sled during all trials, either in darkness or looking at a visual scene projected on a screen. Participants were subjected to each protocol once before intervention, and once after, so as to minimize the effect of habituation. This methodology of provoking the visual and vestibular systems was established in a recently published study.[30] Trials were separated by short breaks of 2–4 minutes allowing the visual and vestibular systems to recover. All stimulations were carried out at 2 motion intensities. Each trial was preceded and followed by 20 seconds of viewing the static visual scene, not presenting any motion. This was done to establish a baseline for each trial. The trials were carried out before and 2 hours after administration of meclizine in order to obtain baseline value of eye-movement parameters that could be compared to the values under the effect of the medication. Eye movement values were compared for both meclizine and placebo treatment groups. While the VOR traditionally is tested through vertical or horizontal head manipulations, this study makes use of a rotational paradigm. This was done as visual and vestibular rotational stimuli share a joint motor output in reflexive

ocular torsion, allowing for comparable stimulation parameters. Additionally, as both visual and vestibular rotations also result in vertical skewing, a typical brainstem reaction to a head tilt, it is evident that torsional movements are heavily ingrained in the human sensorimotor pathways.[30]

2.4 | Visual stimulation

The visual stimulation protocol consisted of oblique white lines on a black background with a central white fixation point (Figure 2). Having established the methodology in a previous study, it was concluded that there was no habituation effect depending on the direction of the visual stimulus.[30] Thus visual scenes were rotated anticlockwise at both low and high intensities. The subject was sitting in the sled facing the screen throughout the trial. The visual stimuli were presented on a projector screen (resolution 1024×768; contrast 2000:1; update frequency 60 Hz) at an eye-screen distance of 2 m. All visual stimulations were preceded by 20 seconds of baseline measure where the image was presented with no movement, allowing the subject to focus on the fixation point. All rotations were performed at 2 intensity levels: $28°/s^2$ (low intensity) and $56°/s^2$ (high intensity) to an amplitude of 14 or 28° respectively.
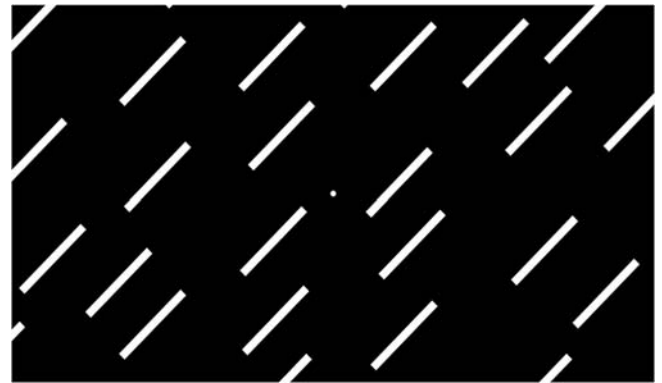
FIGURE 2 The visual stimulus containing 38 white lines 0.42 cm wide and 3.25 cm long (visual angle 0.93°) standing at an angle of 45°. The lines are centred on a round fixation point, 0.32 cm in diameter. The visual scene occupies approximately 50° of the participant's field of vision
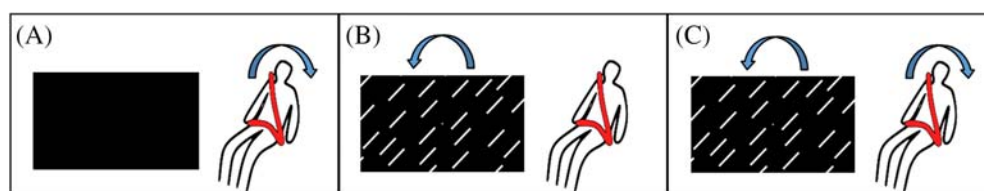
FIGURE 1 The series of sensory balance provocations. All tilts are of the same magnitude and illustrated with a blue arrow indicating tilt-direction. (A) Vestibular stimulation in complete darkness, with the sled being tilted. (B) Visual stimulation with the visual scene being tilted in front of the subject viewing it. (C) Visual–vestibular stimulation with the subject being tilted while viewing the visual scene, relative to the subject's retina, is tilted in the opposite direction

2.5 | Vestibular stimulation

Vestibular stimulation was achieved through full body tilts in complete darkness using a motorized sled, manufactured in house (Figure 3). The sled was tilted in the clockwise direction so as to match the visual rotation. Two separate belts move the sled, moving the top and bottom segments of the chair separately. This allowed for precise rotational (roll) and sideways (translational interaural heave) movements, with the centre of rotation adjustable along the body midline. In this study, the centre of rotation was set to be between the eyes, so as to achieve minimal sideways translational movement and adjusting for differences in height between subjects. During the vestibular stimulation, the room was completely dark to exclude any visual interference on the eye-movement response. To ensure minimal retinal input, the test subjects were exposed to a bright white screen featuring a central black reference point prior to each stimulation. This image was removed without warning, leading to complete darkness and effectively blinding the subject, who was to focus on the afterimage of the black dot after its exposure had ceased. Participants were asked to focus on this imagined target, localized straight ahead. Subjects wore a neck-stabilizer during trials in order to minimize neck movement and proprioceptive input. The subject's head was further stabilized using Velcro straps put through the eye-tracker and fastened to the chair. As the vestibular system is more sensitive to acceleration than the visual system during a head tilt, the vestibular intensity levels were set to half of the visual, i.e. $14°/s^2$ (low intensity), and $28°/s^2$ (high intensity). Both systems are, however, sensitive to changes in amplitudes, meaning that all stimuli amplitudes were set to $14°$ for the low intensity, and $28°$ for the high intensity. As a result, the time of the visual stimulation, 1 second, differ slightly from the vestibular 1.41 seconds. As a result, the eye movement parameters cannot be justifiably compared between sensory modalities, and all analyses are focused on effects within each specific group, i.e. VIS, VES and VIS+VES. As with the visual stimulation, all vestibular stimulations were preceded by 20 seconds of baseline measure.

2.6 | Visual–vestibular stimulation

The visuo-vestibular interaction on the eye-movement response was studied with a parallel administration of vestibular stimuli as previously described, and visual stimulation consisting of a stationary visual field. In this way, the body rotation generated a visual field rotation on the opposite direction with equivalent angular amplitude. The effects of visual and vestibular signalling has been proven additive using this methodology, indicating a sound methodology for testing visual–vestibular integration on the basis of maintaining the same visual and vestibular amplitudes while adopting the visual intensity as a multiple of the vestibular acceleration.[30]

2.7 | Eye and head recording

Eye movements were recorded using the head mounted Chronos Eye Tracker (CET; Chronos Inc, Berlin; Figure 3). Binocular recordings were performed at 100 Hz with a high spatial resolution for horizontal and vertical eye movements (0.05°) as well as ocular torsion (0.1°). The system was calibrated for each subject by having them perform a sequence of eye movements to a pattern of dots with known separations. A head tracking system, consisting of 2 accelerometers, was integrated in the head mask for simultaneous recording of head movements in 6 dimensions (3° of rotation as well as translation). This allows for ensuring that the subject remains still or moving at a precise
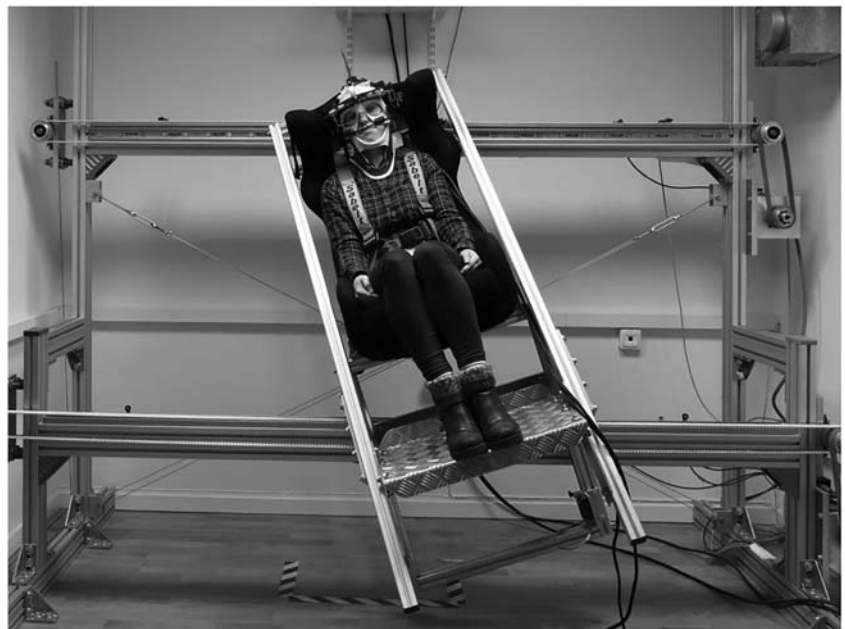
FIGURE 3 The mechanical sled consists of a chair mounted to 2 linear conveyor belts and is manoeuvred by 2 servo-engines. This allows for high-precision linear and rotational movements for vestibular stimulation. The subject is wearing the head mounted eye tracking system (Chronos C-ETD), extrication collar and 4-point seat belt

rate in accordance with the vestibular or visual stimulation prerequisites during the different trials. Torsional eye movements due to mask-slippage or poor video quality has been proven negligible for this type of procedure.[30]

2.8 | Analysis

Eye movement values were carried over to Origin (OriginPro 2017, OriginLab). Analysis was made on either the left or right eye, with the best signal quality being used for retrieving outcome data in terms of torsional velocity and amplitude, i.e. eye position ~5 seconds after each stimulus' stop compared to baseline. The torsional velocity itself was sampled during the slow-phase period of all identifiable slow-phases through the duration of each stimulation and calculated by dividing the change in amplitude of the slow-phase with the duration in seconds.

A full factorial ANOVA analysing the main and interaction effects of *time* (before and after intervention) and *intensity* (low/high) as within-factors and *group* (meclizine/placebo) as a between-group factor was performed. An interaction effect between *time* and *group* was considered a prerequisite for the intervention to have any effect; the *group* signifying the drug administered and *time* the moment at which the measure was taken, i.e. before or after the intervention. By including the factor of *time* the habituation effect of repeated trials could be eliminated as a confounder, as any such phenomenon would be seen in the placebo group. Subsequently, MSSQ score, torsional velocity, amplitude shift and number of nystagmus beats (NB), were compared with respect to these 2 factors, i.e. time and group.

The eyes' torsional velocity has been taken as indicator of SCC-related VOR phasic activity induced by tilting. The utricular activation was assessed through comparing amplitude shifts, i.e. the end position of the eye as compared to its starting point. As for OKN analysis, the average of NB per trial was taken into account as the main indicator of visuomotor pathway integrity. In case of VOR induced torsional nystagmus, the quick phase was denoted as a NB. The beats were identified through visual inspection of the raw torsional traces plotted on a graph.

An initial within-subject analysis yielded the eye movement pattern in response to the different stimulation protocols before and after treatment. Afterwards the subjects were divided into 2 groups according to motion-sickness susceptibility by MSSQ score and their eye movement patterns analysed according to the independent variables *time* and *group*. A repeated ANOVA was applied for the purpose, permitting to reveal interaction effects. Eye movement responses are normally distributed in the general population,[31,32] and ANOVA is considered a stable statistical tool that is not excessively affected by non-normalized data,[33] and considered superior as long as the variable is normally distributed in the parent population.[34] As a complement to the parametric ANOVA, the Bayes factor was calculated using JASP (Version 0.9.2; JASP Team 2019) to obtain the odds for or against the null hypothesis. The BF_{10} value indicates by how much more likely the alternative hypothesis H_1 is than the null hypothesis H_0.[35]

Analysis of eye movement responses were performed for each sensory modality. All comparisons were done on the absolute values for each eye movement response, e.g. NB before drug intervention to NB after, rather than the numerical changes. To increase readability, this study will, however, present the calculated differences in the results between *before* and *after* drug intervention as this provides the clearest information on the effect of meclizine in relation to placebo.

2.9 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[36] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[37]

3 | RESULTS

Meclizine was found to have a significant effect on several eye movement parameters compared to placebo. MSSQ scores were by chance evenly distributed between intervention groups in term of high and low susceptibility and an ANOVA analysis revealing no significant intervention effect related to MSSQ scores. As the data set generally showed a non-normal distribution the complementing Bayesian analysis added valuable context to these findings, generally indicating strong support for the primary findings.

3.1 | Meclizine and eye movement responses

3.1.1 | The effect of meclizine on the vestibular system

Taking the effect in the VES trials into consideration, the result was a significant difference in torsional velocity between the treatment groups, based on changes in OCR before and under the influence of treatment [$F(1,10) = 6.50$; $P = .029$]. Intake of meclizine led to a relative increase in OCR-velocity during vestibular stimulation as compared to the placebo group. No significant difference could be seen for amplitude shift or NB. The Bayesian ANOVA strongly supports a significant effect of meclizine on torsional velocity with an interaction effect between *treatment group*, *time* and *intensity* ($BF_{10} = 1360$).

3.1.2 | The effect on the visual system

There was no significant difference in torsional velocity, amplitude shift or NB during visual stimulation between the meclizine group and the placebo group before and after administration of treatment. The Bayesian ANOVA gives moderate support to maintain H_0 ($BF_{10} = 0.144$).

3.1.3 | The effect on the visual–vestibular system

There was a significant interaction effect for torsional velocity between *time*, *intensity* and *group* during visual–vestibular stimulation [$F(1,10) = 5.14$; $P = .047$], which was strongly supported by the Bayesian factor ($BF_{10} = 195\,535$). Meclizine decreased the torsional velocity during low intensity stimulation compared to placebo and it increased the ocular torsion velocity during high intensity stimulation compared to placebo (Table 1). There was no significant effect between the 2 groups on amplitude shift or NB. There was, however, a distinct difference in NB between stimulus intensity [$F(1,10) = 11.94$; $P = .006$], and time [$F(1,10) = 12.11$; $P = .006$]. The number of NB decreased under the influence of meclizine for VIS+VES, from a mean of 2.92 (1.25) to the mean value of 2.13 (1.48), while an increase of intensity instead led to an increase in NB from 2.17 (1.40) to 2.88 (1.36). The eye movement response of a subject belonging to the meclizine group is represented in Figure 4 for both low and high stimulation intensities. The Bayesian ANOVA gave a strong support for an interaction effect between *time*, *intensity* and *group* on NB ($BF_{10} = 26.900$) and a moderate support for *time* ($BF_{10} = 7.790$) and *intensity* ($BF_{10} = 3.599$).

4 | DISCUSSION

The aim of this study was to evaluate the effect of meclizine, a readily available prescription free motion-sickness medication, on vestibular as well as the visual system by measuring eye movements driven by visual and vestibular provocations. While the study is limited by the number of participants, 6 in the intervention group and 6 in the control group, the results showed a general impact of meclizine on eye movement responses in terms of an increased ocular torsional velocity. The sensory specific trials yielded an increase in velocity for ocular torsion to vestibular stimulation, contradicting the theory of an inhibitory effect on the vestibular system. No significant effects of meclizine could be found regarding visual stimulation on eye movement

parameters. When meclizine was studied in the visual–vestibular trials, a significant effect in term of torsional decrease was observed but restricted to the stimulus lower intensity levels.

4.1 | The effect of meclizine

The pharmaceutical effects of meclizine on the visual and vestibular systems were complex. This phenomenon was highlighted in the rather high standard deviations presented in Table 1, where the changes in eye movement responses before and after intervention are presented. As the MSSQ score were naturally balanced between intervention groups it was made possible to ascertain if the individual level of susceptibility would indicate a better suitability for meclizine. This study found no evidence for such a relationship. Subjective scoring sheets are generally difficult to compare between healthy individuals, and having relatively few subjects makes it difficult to correlate meclizine's antihistaminergic properties to individual improvements based on motion-sickness susceptibility. The main interpretation of these results should instead be that the present study saw no effect of MSSQ score on the intervention effect, and as such we remove individual susceptibility as a possible confounder in interpreting the primary results.

Naturally, there is a certain degree of uncertainty in the clinical interpretations of these results, but regardless of motion-sickness susceptibility there was still a significant effect of the active substance. The reason for this lies in the habituation effect of multiple stimulations, which is further discussed below. This further stresses the value of an ANOVA analysis model, as each intervention can be compared to its baseline for each subject, eliminating the habituation effect in the statistical comparisons. Consequently, the significance levels presented are based on the meclizine effect in relation to the habituation effect, seen for the placebo group. Here we summarize the accredited effects of meclizine on the different subsystem implied in motion perception, according to the results of the present study.

TABLE 1 Difference in eye movement response before and after intervention. Values are presented as mean (standard deviation) for torsional velocity, in °/s, amplitudal shift, in °, and NB, nystagmus beats. The differences give an indication of how the separate subgroups changed regarded to treatment intervention (values after intervention minus values before intervention)

		Low (14°)		High (28°)	
		Meclizine	Placebo	Meclizine	Placebo
Torsional velocity	VIS	−0.25 (0.76)	0.00 (1.24)	0.53 (1.48)	−1.82 (2.65)
	VES	2.36 (7.65)	−0.01 (4.17)	2.61 (6.67)	−3.49 (4.76)
	VIS+VES	−0.40 (3.87)	3.75 (5.62)	3.88 (6.51)	−3.88 (8.55)
Amplitude shift	VIS	−0.28 (0.84)	−0.20 (0.69)	−1.07 (0.67)	0.03 (1.23)
	VES	0.40 (2.86)	−0.93 (1.54)	0.15 (5.10)	−1.70 (3.08)
	VIS+VES	−0.23 (0.93)	−0.42 (2.84)	−1.48 (4.26)	0.98 (4.30)
NB	VIS	0 (1.10)	0.33 (0.82)	−0.67 (1.21)	0.00 (0.00)
	VES	−0.17 (1.17)	0.17 (1.33)	−0.67 (1.21)	0.33 (0.52)
	VIS+VES	−1.50 (1.05)	−0.17 (1.17)	−1.00 (1.27)	−0.50 (1.52)

Abbreviations: VES, vestibular stimulation; VIS, visual stimulation; VIS+VES, visual-vestibular stimulation

(A)

Visual-Vestibular Low Intensity Stimulation

(B)

Visual-Vestibular High Intensity Stimulation
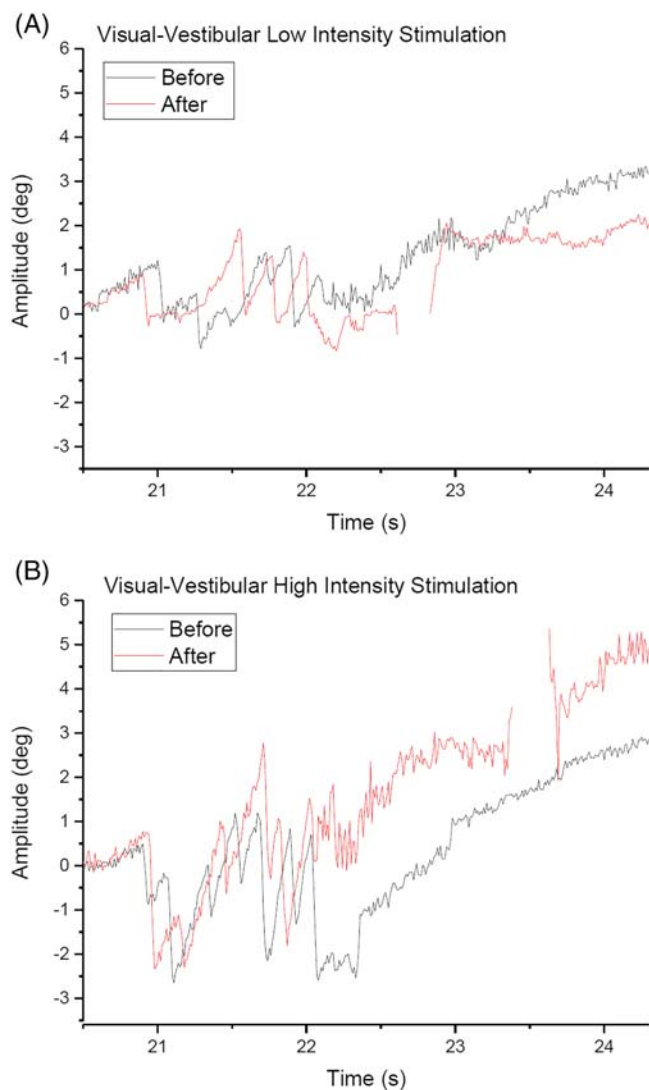
FIGURE 4 The unaltered signal of the torsional response for visual–vestibular during both low ($14°/s^2$) and high ($28°/s^2$) stimulations. Any absence of a signal was due to blinks, but did not interfere with the general analysis

4.2 | Vestibular response

The increased ocular torsion velocity and the nonsignificant change in amplitude shift during vestibular activation in the meclizine group compared to the placebo group contradicts the theory of an inhibition of the vestibular system. More specifically, the increase in torsional velocity indicates that there seems to be no inhibitory effect on SCCs, and the absence of change in amplitude shift indicates that there was no inhibitory effect on the utricle. While contradicting the general hypothesis regarding the effects of meclizine, this is in line with the findings of Dai et al, suggesting no inhibitory vestibular effect.[8]

For the placebo group, there was a general tendency towards a reduced torsional velocity after intervention. Since it is previously known that the vestibular system is sensitive to habituation through both optokinetic[38] and vestibular provocations,[39] one can assume that this reduction is physiological. Conversely, the results of this study seem to support a disinhibitory effect of meclizine on vestibular pathways, as measured in an increased torsional velocity under the influence of the medication. While there is no well-established pharmacological reason for an h1-antagonist to excite such a response on a vestibular level, it has been established that the drug inhibits psychomotor performances.[40]

Weerts et al similarly showed an isolated effect on the SCCs, but in the form of decreased VOR gain, i.e. ratio between eye and head velocities, in the horizontal rotational VOR between placebo and meclizine groups.[12] The SCC stimulation took place in the form of rotational movement around a vertical axis at $3°/s^2$ to a velocity of $400°/s$ during 90 seconds. While all subjects in the Weerts study performed trials with no treatment effect, the effects of meclizine was not compared to baseline for each participants. Instead, the intervention effect was analysed between the meclizine and placebo groups. Additionally, the intervention was in the form of 25 mg meclizine and the trials performed 1.5 hours after administration. In an effort to maximize intervention effects, this study implemented a 2-hour waiting period between administration and trials, so as to allow for maximal plasma levels to be reached, and administered 50 mg meclizine. The repeated ANOVA model used in this study allowed for more in-depth analysis of each intervention group, comparing results during influence of the drug to baseline values.

More importantly, the acceleration implemented in this study was substantially higher, 14 and $28°/s^2$ compared to $3°/s^2$. It is well established that the SCCs are sensitive to acceleration. Consequently, it can be argued that the methodology implemented in this study more readily evaluate the effects of meclizine on the SCCs specifically. Weerts et al[12] state that the main purpose of their stimulation through unilateral centrifugation was to stimulate the utricles, and finding no intervention effects of meclizine, which is in line with our results stating that there was no difference between intervention groups in terms of amplitude shifts.

4.3 | Visual response

Previous studies on the monkey have concluded a reduction of NB gain under meclizine medication.[8] In contrast, this study did not find any effect on meclizine on visually induced oculomotor responses as measured by torsional velocity, amplitude shift and NB. Therefore, according to our results, this study could not support the notion that meclizine affects the visuomotor pathways.

4.4 | Visual–vestibular response

The effect of meclizine on the oculomotor system during combined visual–vestibular stimulation was found to be rather complex. A significant interaction effect for the determinants time (before/after), group

(meclizine/placebo) and intensity (lower/higher stimulus acceleration) was found for torsional velocity.

Even though no separate inhibitory effect was found for the vestibular or visual systems, the decreased torsional velocity during visual–vestibular stimulation at low intensity together with the enhancement at higher stimulation rates for the meclizine group seem to delineate a biphasic oculomotor behaviour in response to stimulus modification under this medication.

These findings highlight the complex pharmacodynamic effects of meclizine. The drug seems to have a quantifiable inhibitory effect on the visual–vestibular ocular reflex only at lower stimulus intensities, and only in case of combined visual–vestibular stimulation. This effect could represent the well stated efficacy of meclizine for motion susceptible subjects in the common motion sickness provocation activities, such as travelling by car or train, which should correspond to the lower intensity stimuli used in these experiment and where both visual and vestibular systems are engaged. For reference, cars in motion are well aligned horizontally, with any movement in the roll plane being very small. Trains often move more at an angle, 5–7° under normal circumstances.[41] The high intensity stimulation of 28°/s^2 can be considered extreme, and generally only experienced systematically in fighter pilots. Modern fighter jets can perform a 90° roll in a couple of seconds,[42] with the maximum steady roll rate being roughly 125°/s.[43] The effectiveness of H1 antagonistic antihistamines have been put to question as a counteragent to motion sickness in aircrew.[44] The results of this study indicate that not only may they be inefficient, they could potentially be counterproductive in that they enhance motion sensitivity.

Consequently, our findings suggest that meclizine has an inhibitory effect on motion sensitivity under normal circumstance, i.e. low intensity roll movements with both the visual and vestibular systems working together. The excitatory effect seen during high intensity stimulation is in agreement with the findings for the isolated vestibular trials. For this reason, one can consider the possibility that meclizine indeed has an effect on the visual–vestibular system to angular acceleration, albeit not specifically on the vestibular flow. Alternate mechanisms for controlling motion-sickness has been suggested before. For example, a study by Tu et al suggested that H1-antagonists affecting the central nervous system by increased brain activity in areas regulating emesis control, and affecting gastric activity.[7] Considering that neither the visual or vestibular systems separately showed any decreased sensitivity to movement, but did so together, may hint at a more centralised top-down mechanism. It can be argued that the synergetic properties of a multisensory balance response results in better information to the brain in how to integrate a complex motion signal. The modulation of this central mechanism may therefore more readily affect motion sensitivity, as compared to regulating each sensory system individually. With regards to the excitatory effect on the vestibular system, and considering that the effects were sensitive to acceleration intensity for a combined visual–vestibular stimuli, it can be argued that the effect on motion sensitivity lies in a system sensitive to angular acceleration other than the vestibular organ, possibly hinting at a more centralized pharmacodynamic mechanism. Instead of

meclizine countering the specific causes of the sensory mismatch, 1 possible interpretation of the results of both Tu et al[7] and this study is that the medication acts on motion sickness by downregulating the integrative function of a multisensory system under sensory mismatch, rather than counteracting specific pathways involved in the multisensory flow. Considering the extended expression of H1 receptors in the body, it could not be excluded that mechanisms other than that studied here could contribute to motion sickness control.

5 | CONCLUSIONS

The aim of this study was to try to give a better insight on the pharmacological effect of meclizine on motion-sickness, which is still controversial. For this purpose, we have studied the effects of visual and vestibular stimulation on eye movement control, especially the effect of meclizine in relation to accelerating stimuli in the roll plane. The recorded eye movement pattern has been studied in terms of ocular torsion velocity, amplitude shifts and NB.

Meclizine resulted in no inhibitory effects on either the visual or vestibular systems. This is in contrast to the current explanation that the antiemetic effects of the drug lies in an inhibition of the vestibular pathways. However, an inhibitory effect was observed in terms of reduced torsional velocity in response to a synergic visual–vestibular stimulation during low intensity stimulation, suggesting that the effectiveness of meclizine on motion sickness relies on central integrative function of the visual–vestibular system. This study supports the use of meclizine for preventing motion-sickness in common environmental conditions, as corresponding to the lower stimulations levels applied in study. Conversely, implementing meclizine in high-acceleration environments, such as those experienced by air combat roles, may be detrimental to the desired effect.

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REFERENCES

1. Reason JT. Motion sickness adaptation: a neural mismatch model. *J R Soc Med*. 1978;71(11):819-829.
2. Money K. Motion sickness. *Physiol Rev*. 1970;50(1):1-39.

3. Lackner JR. Motion sickness: more than nausea and vomiting. *Exp Brain Res*. 2014;232(8):2493-2510.

4. Graybiel A, Wood CD, Miller EF, Cramer DB. Diagnostic criteria for grading the severity of acute motion sickness. *Aerosp Med*. 1968;39(5):453-455.

5. Golding JF. Motion sickness susceptibility. *Auton Neurosci*. 2006;129(1–2):67-76.

6. Shupak A, Doweck I, Gordon CR, Spitzer O. Cinnarizine in the prophylaxis of seasickness: laboratory vestibular evaluation and sea study. *Clin Pharmacol Ther*. 1994;55(6):670-680.

7. Tu L, Lu Z, Dieser K, et al. Brain activation by H1 antihistamines challenges conventional view of their mechanism of action in motion sickness: a behavioral, c-Fos and physiological study in Suncus murinus (house musk shrew). *Front Physiol*. 2017;8:412.

8. Dai M, Kaufmann H, Raphan T, Cohen B. Promethazine affects optokinetic but not vestibular responses in monkeys. *Aviat Space Environ Med*. 2000;71(10):1003-1012.

9. Doweck I, Gordon CR, Spitzer O, Melamed Y, Shupak A. The vestibulo-ocular reflex (VOR) under the influence of cinnarizine. *J Vestib Res*. 1994;4(3):215-220.

10. Weaver CJ. Effect of drugs on ocular counterrolling; 1968.

11. Weerts AP, Vanspauwen R, Fransen E, Jorens PG, Van de Heyning PH, Wuyts FL. Space motion sickness countermeasures: a pharmacological double-blind, placebo-controlled study. *Aviat Space Environ Med*. 2014;85(6):638-644.

12. Weerts AP, De Meyer G, Pauwels G, et al. Pharmaceutical countermeasures have opposite effects on the utricles and semicircular canals in man. *Audiol Neurootol*. 2012;17(4):235-242.

13. Martin N, Oosterveld W. The vestibular effects of meclizine hydrochloride-niacin combination (Antivert). *Acta Otolaryngol*. 1970;70(1):6-9.

14. Cohen B, DeJong JM. Meclizine and placebo in treating vertigo of vestibular origin. Relative efficacy in a double-blind study. *Arch Neurol*. 1972;27(2):129-135.

15. Boussageon R, Vanderkam P, Tudrej B, et al. Clinical efficacy of Acetylleucine, meclozine and betahistine in dizziness: systematic review and meta-analysis of randomiser controlled trials. *Exercer-La Revue Francophone De Medecine Generale*. 2017;133:216-223.

16. Patel PN, Ambizas EM. Meclizine: safety and efficacy in the treatment and prevention of motion sickness. *Clin Med Insights Ther*. 2011;3:CMT.S6237.

17. Golding JF. Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. *Brain Res Bull*. 1998;47(5):507-516.

18. Park DS, Lee G. Validity and reliability of balance assessment software using the Nintendo Wii balance board: usability and validation. *J Neuroeng Rehabil*. 2014;11(1):99.

19. Cardin V, Smith AT. Sensitivity of human visual and vestibular cortical regions to egomotion-compatible visual stimulation. *Cereb Cortex*. 2010;20(8):1964-1973.

20. Waespe W, Cohen B, Raphan T. Role of the flocculus and paraflocculus in optokinetic nystagmus and visual-vestibular interactions: effects of lesions. *Exp Brain Res*. 1983;50(1):9-33.

21. Waespe W, Henn V. Neuronal activity in the vestibular nuclei of the alert monkey during vestibular and optokinetic stimulation. *Exp Brain Res*. 1977;27(5):523-538.

22. Szentágothai J. The elementary vestibulo-ocular reflex arc. *J Neurophysiol*. 1950;13(6):395-407.

23. Pansell T, Tribukait A, Bolzani R, Schworm HD, Ygge J. Drift in ocular counterrolling during static head tilt. *Ann N Y Acad Sci*. 2005;1039:554-557.

24. Vieville T, Masse D. Ocular counter-rolling during active head tilting in humans. *Acta Otolaryngol*. 1987;103(3–4):280-290.

25. Collewijn H, Van der Steen J, Ferman L, Jansen TC. Human ocular counterroll: assessment of static and dynamic properties from electromagnetic scleral coil recordings. *Exp Brain Res*. 1985;59(1):185-196.

26. Pansell T, Sverkersten U, Ygge J. Visual spatial clues enhance ocular torsion response during visual tilt. *Exp Brain Res*. 2006;175(3):567-574.

27. Wibble T, Sodergard U, Traisk F, Pansell T. Intensified visual clutter induces increased sympathetic signalling, poorer postural control, and faster torsional eye movements during visual rotation. *PLoS ONE*. 2020;15(1):e0227370.

28. Holm-Jensen S, Peitersen E. The significance of the target frequency and the target speed in optokinetic nystagmus (OKN). *Acta Otolaryngol*. 1979;88(1–6):110-116.

29. Bronstein A. *Oxford textbook of vertigo and imbalance*. OUP Oxford; 2013.

30. Wibble T, Pansell T. Vestibular eye movements are heavily impacted by visual motion and are sensitive to changes in visual intensities. *Invest Ophthalmol Vis Sci*. 2019;60(4):1021-1027.

31. Clarke H, Schönfeld U, Hamann C, Scherer HA. Measuring unilateral otolith function via the otolith-ocular response and the subjective visual vertical. *Acta Otolaryngol*. 2001;121(545):84-87.

32. Miller EF. Evaluation of otolith organ function by means of ocular counter-rolling measurements; 1969.

33. Alexander RA, Govern DM. A new and simpler approximation for ANOVA under variance heterogeneity. *J Educ Stat*. 1994;19(2):91-101.

34. Lantz B. The impact of sample non-normality on ANOVA and alternative methods. *Br J Math Stat Psychol*. 2013;66(2):224-244.

35. Lee MD, Wagenmakers E-J. *Bayesian cognitive modeling: A practical course*. Cambridge university press; 2014.

36. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY, *Nucleic Acids Research*, 2018;46(D1):D1091–D1106. https://doi.org/10.1093/nar/gkx1121

37. Alexander SPH, Fabbro D, Kelly E, et al. The Concise Guide to Pharmacology 2019/20: Enzymes. *British Journal of Pharmacology*, 2019;176(S1):S297–S396. https://doi.org/10.1111/bph.14752

38. Pfaltz C, Novak B. Optokinetic training and vestibular habituation. *ORL*. 1977;39(6):309-320.

39. Brand J. The effect of repetition on measurements of post-rotational turning sensation and nystagmus in man. *Q J Exp Physiol Cogn Med Sci*. 1968;53(3):312-326.

40. Witek JT, Canestrari DA, Miller RD, Yang JY, Riker DK. Characterization of daytime sleepiness and psychomotor performance following H1 receptor antagonists. *Ann Allerg Asthma Im*. 1995;74(5):419-426.

41. Förstberg J. Ride comfort and motion sickness in tilting trains, Institutionen för farkostteknik; 2000.

42. Paranjape AA, Ananthkrishnan N. Combat aircraft agility metrics-a review. *Aerosp Sci Technol*. 2006;58(2):143-154.

43. Sinha NK, Ananthkrishnan N. Maximum steady roll rate in zero-sideslip roll maneuvers of aircraft. *J Aircr*. 2002;39(5):897-899.

44. Eddy DR, Dalrymple MA, Schiflett SG. Comparative effects of antihistamines on aircrew mission effectiveness under sustained operations. SYSTEMS RESEARCH LABS INC DAYTON OH;1992.