Clinical Biomechanics 96 (2022) 105671

Contents lists available at ScienceDirect

Clinical Biomechanics

journal homepage: www.elsevier.com/locate/clinbiomech

Original Articles

Motion sickness decreases low back function and changes gene expression in military aircrew

Jonathan S. Dufour [a], Ali Reiter [b], Cyndy Cox [c], Eric B. Weston [a], Michael Markey [d], Ashley Turner [c], Peter Le [e], Alexander M. Aurand [a], Stacy Simmons [d], Lorenna Altman [c], Prasath Mageswaran [a], Kermit Davis [c], Dustin Huber [f], Amit Bhattacharya [c], William S. Marras [a,*]

[a] Spine Research Institute, The Ohio State University, Columbus, OH, USA
[b] Wright State Research Institute, Dayton, OH, USA
[c] Department of Environmental and Public Health Sciences, University of Cincinnati, Cincinnati, OH, USA
[d] Department of Biochemistry and Molecular Biology, Wright State University, Dayton, OH, USA
[e] Naval Medical Research Unit – Dayton, Dayton, OH, USA
[f] Navy Medicine Operational Training Center, Patuxent River Detachment, Patuxent River, MD, USA

ARTICLE INFO

Keywords:
Kinetosis
Lumbago
Standing balance
microRNA

ABSTRACT

Background: Motion sickness and low back disorders are prevalent and debilitating conditions that affect the health, performance, and operational effectiveness of military aircrews. This study explored the effects of a motion sickness stimulus on biomechanical and genetic factors that could potentially be involved in the causal pathways for both disorders.

Methods: Subjects recruited from a military population were exposed to either a mild ($n = 12$) or aggressive ($n = 16$) motion sickness stimulus in a Neuro-Otologic Test Center. The independent variable of interest was the motion sickness stimulus exposure (before vs. after), though differences between mild and aggressive stimuli were also assessed. Dependent measures for the study included motion sickness exposure duration, biomechanical variables (postural stability, gait function, low back function, lumbar spine loading), and gene expression.

Findings: Seven of twelve subjects experiencing the mild motion sickness stimulus endured the full 30 min in the NOTC, whereas subjects lasted an average of 13.2 (SD 5.0) minutes in the NOTC with the aggressive motion sickness stimulus. Mild motion sickness exposure led to a significant decrease in the postural stability measure of sway area, though the aggressive motion sickness exposure led to a statistically significant increase in sway area. Both stimuli led to decreases in low back function, though the decrease was only statistically significant for the mild protocol. Both stimuli also led to significant changes in gene expression.

Interpretation: Motion sickness may alter standing balance, decrease low back function, and lead to changes in the expression of genes with roles in osteogenesis, myogenesis, development of brain lymphatics, inflammation, neuropathic pain, and more. These results may provide preliminary evidence for a link between motion sickness and low back disorders.

1. Introduction

Motion Sickness (MS) and Low Back Disorders (LBDs) are prevalent and debilitating conditions affecting the health, performance, and operational effectiveness of military aircrews (Catanzariti et al., 2016; Cohen et al., 2009; Hartvigsen et al., 2018; Orsello et al., 2013; Wertheim, 1998). Estimations of aviator MS prevalence range from 10 to 38%, but in extreme conditions, incidence rates can be as high as 50–90% (Dobie, 2019; Simmons et al., 2008). Similarly, the prevalence of LBDs in military populations ranges from 33 to 58% (Bader et al., 2018; Harrison et al., 2015). While the symptoms of both MS and LBDs are quite different, anecdotal evidence from military officials suggests that military service members who suffer from MS may be significantly more likely to also suffer from a LBD. If this is true, the identification of

* Corresponding author at: 1971 Neil Avenue, Room 520, Columbus, OH 43210, USA.
E-mail address: marras.1@osu.edu (W.S. Marras).

https://doi.org/10.1016/j.clinbiomech.2022.105671
Received 7 May 2021; Accepted 11 May 2022
Available online 15 May 2022

factors that influence both MS and LBDs could allow for the development of screening tools that are helpful at identifying at risk individuals and countermeasures that are helpful for prevention and treatment of both disorders.

To the authors' knowledge, a direct relationship between MS and LBDs has yet to be formally investigated in the scientific literature. However, the scientific literature does provide evidence of biomechanical causes for both disorders, which could suggest why some overlap between them has been noted anecdotally. The dominant account for the etiology of MS is sensory conflict theory, which suggests that the central nervous system (CNS) has an internal model that makes predictions of motion and sensory patterns based on incoming afferent signals (visual, vestibular, somatic) and past experiences. When there is incongruence between incoming afferent signals and predictions being made by internal model, MS symptoms are expected to be provoked (Reason and Brand, 1975; Warwick-Evans et al., 1998). However, this dominant theory has also been challenged by a secondary theory called the postural instability theory of motion sickness, which suggests more of a biomechanical basis for MS (Riccio and Stoffregen, 1991). According to this theory, MS arises from situations in which animals do not possess (or have not yet learned) strategies that are effective for the maintenance of postural stability. By extension, the greater the duration of the postural instability, the greater the likelihood and predicted severity of motion sickness. Thus, MS symptoms form a continuum rather than being all-or-none (Riccio and Stoffregen, 1991). Moreover, the postural instability theory of motion sickness suggests that MS is inherently a result of behavior (i.e., postural control) rather than sensory stimulation (although sensory afferents are not completely removed from this theory given that overall body posture is also affected by these signals).

Likewise, a load-tolerance approach suggests that the relationship between tissue load and its corresponding tissue tolerance may define the risk of experiencing a LBD (Marras, 2012). According to this logic, when peak forces on the intervertebral discs of the spine are below what the tissue can handle, a given activity can be considered safe. However, when peak forces exceed the tissue tolerance, then risk for a LBD is present for at least some proportion of the population (Marras, 2012). Loading on the spinal tissues can be triggered by physical work factors, individual factors, or by psychosocial or organizational factors (NRC, 2001). All of these factors can influence the response (i.e., coactivity) of the power-producing muscles of the trunk, wherein muscle coactivity has been linked to reduced low back function and increased forces on the spine (Granata and Marras, 1995; Marras et al., 2001).

If biomechanical factors associated with both MS and LBDs are related, then it is reasonable to assume that these disorders are also indeed related to one another. For example, it is reasonable to believe that when postural stability is impaired, the body would compensate via altered neuromuscular recruitment patterns that help to maintain greater postural stability, particularly muscle coactivity and "guarding" behavior, which as stated above are known risk factors for the development of LBDs (Ferguson et al., 2009; Marras, 2012). Alternatively, the link between MS and LBDs may be even more direct than the pathway stated here. A complementary or entirely separate explanation may be related to a shared genetic influence that could be driving the relationship between MS and LBDs (Hromatka et al., 2015).

To explore the potential link between MS and LBDs, the objective of this study was to quantify the effects of a MS stimulus on biomechanical (i.e., postural stability, gait function, low back function, lumbar spinal loading,) and genetic factors (circulating small RNA expression) potentially associated with both conditions in a military population. The central hypothesis was that some underlying covariate(s) link both disorders.

2. Methods

2.1. Approach

A laboratory study was conducted to better understand the effects of a MS stimulus on postural stability, gait function, low back function, lumbar spine loading, and circulating small RNA expression. In this laboratory study, subjects were exposed to one of two MS protocols (mild or aggressive), and dependent variables from each of the aforementioned domains were assessed before and after exposure to the MS stimulus. The effects of both mild and aggressive MS protocols were assessed separately, but potential differences between the protocols were also assessed to account for a potential dose-response relationship between MS severity and the dependent measures. Sex-based differences were also assessed.

2.2. Subjects

Twelve subjects (8 male, 4 female) were exposed to the mild MS stimulus, and sixteen subjects (9 male, 7 female) were exposed to the aggressive MS stimulus. Age, stature, and mass characteristics for each group of subjects (by sex and protocol) are shown in Table 1 below. All subjects were asymptomatic for LBDs as well as other musculoskeletal disorders, and demographics were similar across the two MS stimulus groups. The study protocol was approved by all respective University and Institutional Review Boards in compliance with all applicable federal regulations governing the protection of human subjects.

2.3. Procedure and motion sickness stimuli

After arrival, subjects provided written informed consent, and a pregnancy test was obtained for female subjects to ensure no pregnant women participated. After collecting basic anthropometric measures, subjects were instrumented with IMU sensors (used to assess postural stability and gait function), electromyography (EMG) sensors (used to assess lumbar spinal loading), and motion capture markers (used to asses lumbar spinal loading), described further below. Though not all sensors were required for every test, sensors remained mounted to the subject whenever feasible (including inside the NOTC) to decrease the amount of down-time and optimize subject comfort throughout the study (with exception for the Clinical Lumbar Motion Monitor mentioned below, which was easy and quick to don and doff). Once instrumented, baseline data were collected across the previously mentioned domains including: postural stability, gait function, low back function, lumbar spine loading, and small RNA expression (described in more detail below). These data were used to represent the state of the subject before exposure to the MS stimulus. The testing order of these first four domains was randomized across subjects, but small RNA expression was always performed last because it involved a blood draw. It should also be noted that the data from all these domains were collected in a common data collection area. That is, subjects were not traveling from room to room to collect all these necessary data.

Table 1
Demographic characteristics of the subjects. Values are represented as mean (standard deviation).

	Age (years)	Stature (cm)	Mass (kg)
Mild Stimulus			
Males (n = 8)	35.1 (4.4)	181.3 (4.7)	88.4 (8.1)
Females (n = 4)	30.8 (6.8)	165.4 (9.0)	69.4 (9.2)
All Subjects (n = 12)	33.7 (5.4)	176.0 (9.9)	82.0 (12.3)
Aggressive Stimulus			
Males (n = 9)	27.7 (5.5)	183.1 (6.7)	85.7 (11.6)
Females (n = 7)	30.7 (9.9)	165.8 (8.2)	71.0 (17.8)
All Subjects (n = 16)	29.0 (7.6)	175.5 (11.4)	79.3 (16.0)
Both Protocols (N = 28)	31.0 (7.0)	175.7 (10.6)	80.4 (14.4)

Once all baseline data were collected, subjects were led just down the hall (approximately 100 ft away) from the data collection room and exposed to one of two MS stimuli (mild, aggressive) via a I-Portal Neuro-Otologic Test Center (NOTC) (Neuro Kinetics, Inc., Pittsburgh, PA, USA). The NOTC is commercially available, computer controlled, servo-driven, and capable of producing simultaneous controlled motion in the yaw and pitch axes. Various spin profiles can be produced, saved, and replicated and allow for input of motion control parameters including direction of rotation, acceleration, velocity, and duration. As such, this device is often used in both clinical and other research settings (Kim et al., 2021).

During the MS stimulus, subjects were seated inside a light-proof, closed chamber (i.e., no interior illumination or windows). A two-way headphone and microphone system worn by the subjects allowed for constant communication between the operator and subject. For the mild MS stimulus protocol, subjects were tilted to an angle of 30 degrees. The platform was then rotated clockwise at a speed of 10 rpm for up to 30 min to elicit MS symptoms (Dai et al., 2010). In contrast, for the aggressive MS stimulus protocol, subjects were not tilted in the NOTC, but were asked to tilt their head laterally from neutral position (0 degrees), to left (30 degrees), to right (30 degrees), and back to neutral at a rate of 0.1 Hz (Lawson et al., 2009). While tilting their heads, subjects were rotated clockwise at a speed ranging from 1 to 40 rpm for up to 40 min, and the speed of the rotation was increased by 1 rpm every minute. In both MS protocols, subjects were instructed to keep their eyes open and were restrained in the chair at the chest, waist, and ankles. However, the head and neck motion were not restrained.

Subjects were rotated in the NOTC until they expressed that they were sick, though the stopping criteria varied between the mild and aggressive MS protocols. For the mild MS protocol, a verbal cue of mild stomach awareness (yes/no) reported by the subject was used as the stopping criterion. In contrast, for the aggressive protocol, a verbal cue of moderate nausea (at least 5 on a 0–10 scale) reported by the subject was used as the stopping criterion. These stomach awareness and nausea ratings were assessed during the final 15 s of each minute of rotation while inside the NOTC via verbal communication with the subject. Prior to experiencing the MS stimulus, subjects were briefed on a symptom profile derived from the Pensacola Motion Sickness Questionnaire (MSSQ) (Hutchins Jr. and Kennedy, 1965) to guide their self-report of common motion sickness symptoms. Using MSSQ as a guide to rate symptoms helped to ensure consistency in the termination point for individual subjects and between all subjects.

After the MS stimulus, subjects were removed from the NOTC, placed into a wheelchair for their safety, and wheeled back to the data collection area. Data were once more collected across the five domains of interest for each subject in the same order as before the MS stimulus.

2.4. Dependent variables

As mentioned, dependent measures for this study encompassed broad domains of postural stability, gait function, low back function, lumbar spinal loading, and circulating small RNA expression (see Table 2). All of these dependent measures were assessed pre- and post-exposure to the MS stimulus but not during exposure in the NOTC. Measures of exposure duration (i.e., how long subjects were in the NOTC before experiencing MS symptoms) and MS severity (i.e., nausea ratings from the aggressive MS stimulus) were also reported herein.

2.4.1. Postural stability

When assessing postural stability, subjects performed two balance tasks (the order of conditions counterbalanced) while standing on an AMTI force platform (Accusway Plus, Advanced Medical Technology Inc. Watertown, MA, USA) and wearing a wireless IMU affixed to the chest. These balance conditions included standing with eyes open on a stable force platform (EO) and standing with eyes closed on a foam platform (ECF). Standing balance trials lasted 30 s, and two repetitions of each condition were collected. During each trial, the movement of the subject on the force platform was used to calculate the instantaneous center of pressure (COP), and COP was used to derive the variables in Table 2. Dependent measures reported herein represent the average of the repetitions collected for each subject, with each trial type (EO, ECF) analyzed separately.

Following each static balance trial, subjects also rated their perceived sense of postural instability (PSPSI). The PSPSI scale, originally described by Chiou et al. (1998), asks subjects to rate their perceived instability for four items on a scale from 0 to 2. Subjects rate 1) how much they felt their body sway, 2) how much difficulty they had maintaining balance, 3) if at any time they felt that they would fall, and 4) the overall difficulty of the task. Each item's scores are summed such that the overall score ranges 0–8, where 8 represents the greatest PSPSI and 0 represents the minimum rating. This scale has been validated as reproducible and has been shown to be sensitive to changes in both the external environment (e.g., surface firmness, lighting) and experimental task (Chiou et al., 1998).

2.4.2. Gait function

Gait function was assessed via a modified version of the Instrumented Timed Up and Go test (iTUGT) (Zampieri et al., 2010; Zampieri et al., 2011). During the test, data were collected from IMUs (Yost Labs, Portsmouth, OH, USA) affixed to the chest, wrists, and shanks. For

Table 2
Dependent measures of interest for the study.

Domain	Dependent variable	Description	Equipment	Assessed
Exposure Duration	Duration of MS Exposure	Measured in minutes	NOTC	Inside NOTC
	Peak nausea (aggressive MS)	Score (0 or 1 in mild MS, 0–10 in aggressive MS)		
Postural Stability	Sway length	Measured in cm	AMTI Force Platform, wireless IMU on chest	Pre/post MS exposure
	Sway area	Measured in cm^2		
	Mediolateral sway	Measured in cm		
	Anteroposterior sway	Measured in cm		
	Perception of instability (PSPSI)	Score (0–8)		
Gait Function	Turn duration (TD)	Measured in seconds	YostLabs wireless IMUs	Pre/post MS exposure
	Cadence	Measured in steps/min		
	Single stance time	Measured in seconds		
	Double support time	Measured in seconds		
	PSPSI	Score (0–8)		
Low Back Function	Probability of normal lumbar function (Pn)	Probability (range 0–1)	Clinical Lumbar Motion Monitor (cLMM)	Pre/post MS exposure
Lumbar Spine Loading	Peak resultant lumbar spine load	Measured in Newtons	OptiTrack motion capture system, Delsys Trigno EMG system, Bertec force plate	Pre/post MS exposure
Gene Expression	Small RNA	Normalized fluorescent signal intensity	Affymetrix microarray station, QuantStudio 7 thermocycler	Pre/post MS exposure

subjects experiencing the aggressive stimulus, additional sensors were worn around the shins, thighs, and waist (LEGSys, BioSensics, Newton, MA, USA). Accelerometer and gyroscope data were utilized to calculate the variables described in Table 2 using a method described previously (Bhattacharya et al., 2016).

In the iTUGT, subjects were asked to arise from a chair, walk 6 m, turn, and walk back, taking two laps before sitting back down. Subjects were asked to walk as quickly but as safely as possible, and stopwatch times for each test were recorded. Two conditions were also tested, including single-task (ST) and dual-task (DT). ST trials were completed as outlined above, while DT trials added an additional cognitive demand in which subjects were assigned a number between 500 and 700 at the beginning of the trial and were instructed to repeatedly subtract 3 from this number out loud for the duration of the test, comparable to the math portion of the Trier Social Stress Test (Montero-Odasso et al., 2012). Each subject performed 3 trials of each condition in the following order: ST, ST, DT, DT, DT, and ST. An average of the dependent measures across the three trials was used for statistical testing, and each trial type (ST, DT) was analyzed separately. Finally, as was performed with the postural stability trials, PSPSI ratings were also gathered after each trial and averaged across the ST and DT conditions here as well.

2.4.3. Low back function

Low back function was assessed using a Clinical Lumbar Motion Monitor (cLMM), which is a wearable motion sensor system that utilizes two inertial measurement unit (IMU) sensors affixed to the body via shoulder and waist harnesses. The cLMM test protocol utilizes three-dimensional kinematic trunk motions to generate a functional impairment score that is normalized for age and gender. Functional impairment scores range from 0.00 to 1.00, with scores above 0.60 indicating healthy function. The cLMM and testing procedure have been described extensively in the literature (Ferguson et al., 2003; Ferguson et al., 2009; Marras et al., 1994; Marras et al., 1995; Marras et al., 1999; Marras et al., 2000; Marras and Wongsam, 1986).

2.4.4. Lumbar spine loading

To assess lumbar spine loading, a 9.07 kg medicine ball was placed in front of the subject at knee height, approximately 40 cm away from the body. Subjects were asked to lift the weight at a comfortable pace while keeping their feet in a fixed position, and each lift was performed twice. The peak resultant lumbar spinal load was calculated using a validated EMG-assisted biomechanical model and extracted as the dependent measure of interest (averaged across repetitions). This EMG-assisted model used in this study to estimate lumbar spine loads has been described previously (Dufour et al., 2013; Hwang et al., 2016a; Hwang et al., 2016b) and is unique because trunk muscle responses during dynamic activities are used to capture the effects of realistic muscle co-activation when estimating spinal loads. The model relies on dynamic inputs of whole body kinematics (assessed via motion capture), torso muscle activations (assessed via EMG), and kinetic data (collected from a force plate). Whole body kinematics were captured using a 16-camera OptiTrack optical motion capture system (Prime 13, NaturalPoint, Corvallis, OR, USA) in conjunction with forty-one reflective markers placed onto the body consistent with a custom marker set prescribed by the motion capture software. Muscle activations were collected using a Delsys Trigno (Delsys Inc., Natick, MA) wireless electromyography system, with electrode pairs placed bilaterally on the ten power-producing trunk muscles (Mirka and Marras, 1993). Finally, kinetics were captured as subjects stood on a Bertec 4060 Force Plate (Bertec, Worthington, OH, USA) during the lifting exertions.

2.4.5. Gene expression

Gene expression was measured from peripheral blood draws using an Affymetrix microarray station (Affymetrix, Santa Clara, CA, USA). Single nucleotide polymorphisms were genotyped using a QuantStudio 7 real-time thermocycler (Thermo Fisher Scientific, Waltham, MA, USA). To assess circulating small RNA expression, 10 mL of blood was collected in red-capped tubes (no anticoagulant, Becton Dickinson, Franklin Lakes, NJ) and allowed to clot at room temperature for 30 min post draw. Tubes were centrifuged 20 min at 2000 xg at 4 °C to precipitate cellular material, and supernatant was removed and transferred to cryotubes for RNA isolation. Additionally, 4 mL of blood was collected into lavender-topped tubes (potassium EDTA, Becton Dickinson, Franklin Lakes, NJ) and transferred to separate cryotubes for DNA isolation. All blood specimens were stored at −80 °C prior to nucleic acid isolation.

The blood samples were analyzed for circulating small RNAs, including miRNAs. Total circulating RNA (primarily miRNA and other small RNA) from 200 μL of serum was isolated and purified with miRNeasy Serum/Plasma Kit (QIAGEN, Frederick, MD, USA). RNA quantity was measured using an Agilent Small RNA Kit on an Agilent 2100 Bioanalyzer (Agilent, Santa Clara, CA, USA). A FlashTag™ Biotin HSR RNA Labeling Kit (Thermo Fisher Scientific, Waltham, MA, USA) was used according to the manufacturer's protocol for miRNA labeling. Labeled samples were hybridized on GeneChip™ miR4.0 Arrays, washed per manufacturer's instructions with a GeneChip Hybrization, Wash, and Stain Kit on a GeneChip® Fluidics Station, and then scanned on a GeneChip Scanner 3000 (Affymetrix, Santa Clara, CA, USA). Scanned chip images were then analyzed by Transcriptome Analysis Software v. 4.0.1 (Affymetrix, Santa Clara, CA, USA). Data summarization was performed by RMA + DABG for the human content of the arrays. Annotation was performed using the most recent version for these arrays (miR-4.0-st-v1.annotations.20160922.csv). Gene expression was filtered by fold-change of at least 1.2, gene-level p-value of less than 0.05, and DABG$<$0.05.

A targeted analysis of single nucleotide polymorphisms (SNPs) associated with MS was conducted using blood DNA. DNA was extracted and purified from 200 μL of peripheral blood using a GeneJet Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, Waltham, MA, USA). The quantity and quality of the DNA extracted was determined using a Nano Drop One spectrophotomer (Thermo Fisher Scientific, Waltham, MA, USA). Of interest were forty-eight single nucleotide polymorphisms (SNPs) associated with motion sickness (Hromatka et al., 2015) or in genes controlling epigenetic modification. Genotyping was performed with Taqman allele discrimination assays per manufacturer's instructions with a QuantStudio 7 Flex (Applied Biosystems, Waltham, MA, USA) polymerase chain reaction system by measuring the fluorescence signals for VIC and FAM in each well, which corresponds to each allele. Taqman Genotyper Software (Applied Biosystems, Waltham, MA, USA) was used for genotype determination.

2.5. Statistical analysis

First, variables collected while inside the NOTC (MS exposure duration, nausea severity) were described. Given that the exposure data were not normally distributed, a nonparametric Mann Whitney U test was conducted to determine whether exposure duration or nausea severity varied between the male and female subjects in each protocol. Then, the effects of the two MS stimuli (mild, aggressive) on the other dependent measures (biomechanical, gene expression) were considered. As mentioned, the primary comparison of interest for these variables was the MS stimulus exposure (before vs. after), and the effects of each of the two MS stimuli (mild, aggressive) were evaluated separately. However, these data were also evaluated for potential differences between the mild and aggressive protocols and potential differences between males and females in a secondary analysis.

To prepare the biomechanical variables (posture, gait, low back function, spinal loading), for statistical analysis, each of the dependent measures was first inspected visually to confirm that the data were approximately normally distributed. Data points with values above/below the upper/lower quartile (respectively) by any more than 1.5 times the interquartile range were excluded as outliers. Then, paired t-

tests were conducted to evaluate whether differences existed in the dependent measures before versus after the MS stimulus.

Likewise, for small RNA expression, normalized signal intensities after MS stimulus were compared to their matched controls prior to stimulus. For SNP analysis, genotypes significantly outside of Hardy-Weinberg equilibrium for the study population ($p < 0.05$) were excluded from further analysis. The top and bottom quartiles for dependent variables were compared by chi-square analysis to determine if any genotypes were significantly more or less common in those groups.

For variables for which a statistically significant difference was observed pre- versus post-exposure to the MS stimulus, Pearson's correlation coefficients were calculated from paired observation changes to determine the degree of covariance between measures from different domains; the statistical significance of each pairwise correlation coefficient was also assessed. Additional analyses were also performed on these variables to determine if significant differences existed based on either MS stimulus severity (mild vs. aggressive) or sex (male vs. female). These analyses were performed as Mann-Whitney *U* tests, which compared the changes in the medians of the dependent measures for the mild versus aggressive protocols and for males versus females within each MS protocol. All statistical tests were performed using JMP 14.0 Pro software (SAS Institute Inc., Cary, NC, UA) relative to a significance level (α) of 0.05.

3. Results

3.1. Exposure duration

Seven of twelve subjects (6 male, 1 female) made it through the full mild MS protocol without surpassing the stopping criteria (stomach awareness of 1). The other five subjects experienced motion sickness rather quickly and stopped the MS stimulus after durations of 2–14 min. Exact exposure durations included 2 min (female), 4 min (female), 4 min (male), 7 min (male), and 14 min (female). In contrast, none of the sixteen subjects lasted the full 40 min of the aggressive MS protocol before surpassing the stopping criteria (nausea rating of 5 or higher). Exposure duration and peak nausea ratings for the subjects experiencing the aggressive MS stimulus are shown in Table 3 below. Neither exposure duration for the mild or aggressive stimuli nor peak nausea ratings (aggressive MS protocol) varied according between males and females.

3.2. Biomechanical

Results of the paired t-tests for each of the biomechanical measures shown in Table 4. The MS stimulus affected postural stability measures of sway area (both MS stimuli), mediolateral sway (aggressive MS stimulus), and perceived sense of postural instability (PSPI) (aggressive MS stimulus). The MS stimulus also influenced low back function (mild MS stimulus only). However, it did not influence lumbar spine loading ($p = 0.472$ for the mild stimulus and $p = 0.127$ for the aggressive stimulus) or any of the gait function variables (turn duration, single stance time, double stance time, cadence, PSPI).

Regarding postural stability, neither the mild nor aggressive stimulus affected any of the postural sway variables for the eyes open (EO) condition. However, both MS stimuli significantly influenced SA in both protocols for the eyes closed foam (ECF) condition ($p = 0.030$ for the mild stimulus and $p = 0.039$ for the aggressive stimulus). As shown in Fig. 1, the direction of the effect differed based on the stimulus protocol (mild vs. aggressive), leading to a statistically significant difference between the protocols in the Mann-Whitney *U* test ($p < 0.001$). SA decreased significantly on average following the mild MS stimulus protocol. However, the aggressive MS stimulus led to a significant increase in sway area. Changes to sway area did not differ between male and female subjects for either the mild or aggressive MS stimuli.

While subjects' perceived sense of postural instability (PSPI) was unaffected by the mild MS stimulus, subjects perceived significantly greater sway for both the EO ($p = 0.05$) and ECF ($p = 0.008$) conditions following the aggressive MS stimulus, with average PSPI scores increasing by 0.438 and 0.797 for EO and ECF conditions, respectively. As with SA results, changes to PSPI scores did not differ between male and female subjects.

Regarding low back function, most subjects experienced a decrease in Pn after exposure to the MS stimulus (average reduction of 0.07 for mild MS stimulus and 0.05 for the aggressive MS stimulus). Changes in Pn after each MS protocol are shown in Fig. 2. The observed reduction in Pn was statistically significant for the mild MS stimulus ($p = 0.008$), but not for the aggressive stimulus ($p = 0.130$). The Mann-Whitney *U* test showed that the change in Pn after the MS stimulus did not differ significantly between the mild and aggressive protocols ($p = 0.715$). Additionally, changes to Pn did not differ between male and female subjects.

Table 3
Exposure duration and peak nausea ratings for aggressive MS stimulus. Values are represented as mean (standard deviation).

Aggressive stimulus	Exposure duration (min)	Peak nausea rating (0–10)
Males (n = 9)	13.0 (6.2)	7.7 (1.7)
Females (n = 7)	13.4 (3.2)	7.9 (1.2)
All Subjects (n = 16)	13.2 (5.0)	7.8 (1.4)

Table 4
Statistically significant results of the MS stimuli in biomechanical variables.

Domain	Dependent variable	Effect of MS stimulus
Postural Stability	Sway length	
	Sway area	* (mild) * (aggressive)
	Mediolateral sway	
	Anteroposterior sway	
	Perception of instability (PSPSI)	* (aggressive)
Gait Function	Turn duration (TD)	
	Cadence	
	Single stance time	
	Double support time	
	Perception of instability (PSPSI)	
Low Back Function	Pn	** (mild)
Lumbar Spine Loading	Peak resultant lumbar spine load	

* Denotes a statistically significant change $p < 0.05$, while ** denotes $p < 0.01$.

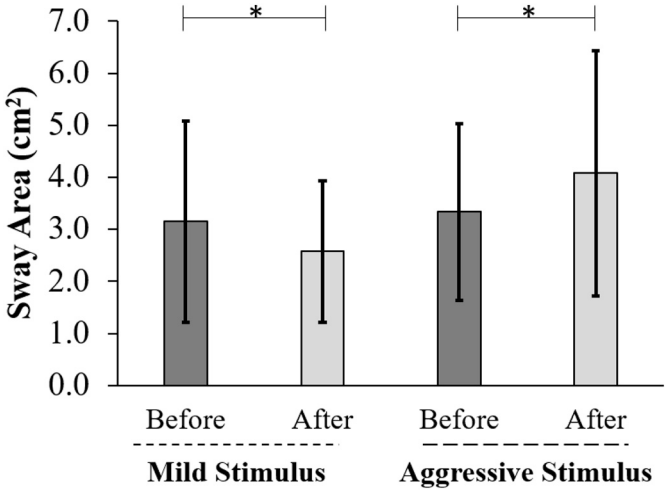

Fig. 1. Sway area (postural stability) before and after mild and aggressive MS stimuli for the eyes closed foam (ECF) experimental condition. Error bars denote standard deviation, while * denotes a statistically significant difference at a significance level 0.05.

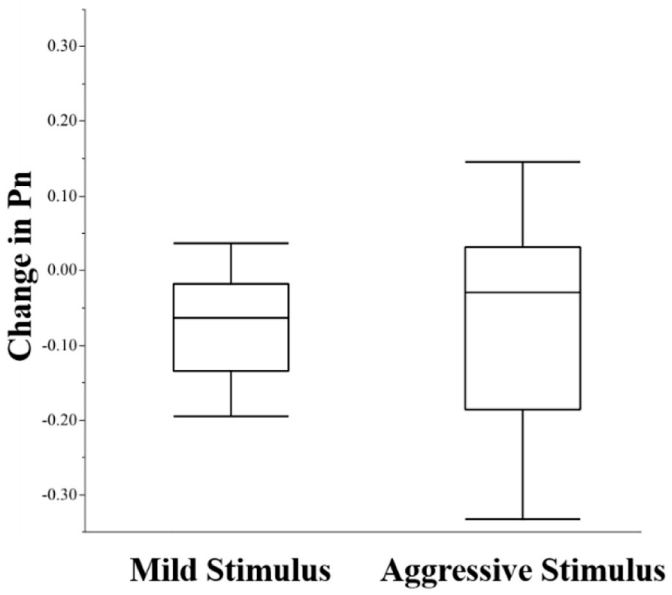

Fig. 2. Box-and-whisker plot showing the change in low back function (Pn) after both mild and aggressive MS stimuli.

3.3. Gene expression

Results of the chi-square analysis performed relative to changes in circulating small RNA expression are shown in Table 5. As shown, the mild MS stimulus led to 19 miRNAs with statistically significant changes ($p < 0.03$) in expression (>1.2-fold or < −1.2-fold) before and after the MS protocol. Likewise, 6 other miRNAs were identified with statistically significant changes ($p < 0.01$) in expression for MS-exposure using the aggressive MS stimulus. These miRNAs play roles in cellular processes including osteogenesis, bone homeostasis, inflammation, differentiation of myoblasts and osteoblasts, and neuropathic pain pathways. No significant correlations were found between individual SNP genotypes and other variables, although the major (C) allele of rs1378552, was more common than expected in subjects in the bottom quartile of Low Back Function (Pn) values ($\chi^2 = 3.89$, $p = 0.049$).

Table 5
Statistically significant acute changes in circulating small RNA expression following MS stimulus.

Transcript ID	Fold change	*p* value
hsa-miR-3157-3p	−1.38	<0.001
hsa-mir-16-2	1.26	<0.001
hsa-miR-324-3p	1.53	<0.001
hsa-miR-1207-5p	−1.23	<0.001
hsa-miR-4787-3p	−1.21	<0.001
hsa-miR-6798-3p	−1.21	<0.001
hsa-miR-550b-3p	1.22	0.002
ENSG00000252719	−1.2	0.002
hsa-miR-4305	1.21	0.002
hsa-miR-548 ac	1.44	0.003
hsa-miR-548a-3p	1.68	0.005
hsa-miR-202-5p	−1.24	0.006
hsa-miR-3150b-5p	1.22	0.006
hsa-mir-4453	−1.24	0.010
hsa-miR-4739	1.23	0.011
hsa-miR-6765-5p	−1.31	0.011
hsa-miR-122-5p	−1.27	0.012
U96a	1.25	0.013
hsa-miR-6797-3p	−1.31	0.015
hsa-mir-101-1	1.21	0.016
hsa-miR-3190-5p	1.32	0.017
hsa-miR-32-5p	−1.29	0.017
hsa-miR-4663	1.3	0.027
hsa-miR-4508	1.49	0.029
hsa-miR-4532	1.64	0.049

3.4. Pairwise correlations

Finally, a significant pairwise correlation was found between Sway Area induced by the mild MS protocol and levels of circulating U96a (correlation coefficient = 0.5785, $p = 0.049$). This small nucleolar RNA is typically found in Cajal bodies, but is also known to play a role in insulin-mediated signaling (Revilla et al., 2013).

4. Discussion

Motion sickness (MS) and low back disorders (LBDs) represent complex conditions that can affect a variety of systems in the body and lead to pain, discomfort, and decreased quality of life. Both disorders are highly prevalent in military populations, and anecdotally, military service members who have one condition have been noted to be significantly more likely to suffer from the other. The potential relationship between motion sickness and low back pain has yet to be investigated formally, though shared biomechanical and/or genetic factors related to the etiology of both disorders might help to explain this previously observed overlap between both conditions. To test this hypothesis, this study quantified the effects of two MS stimuli (mild and aggressive) on factors including postural stability, gait function, low back function, lumbar spinal loading, and circulating small RNA expression. The results of this study suggest that MS can alter standing balance, which may lead to decreased low back function. MS may also lead to changes in circulating miRNAs controlling a diverse range of target mRNA expression. Interestingly, no sex-based differences were observed herein. In contrast, prior studies have shown that standing body sway and motion sickness exposure duration vary between males and females (Kim et al., 2010; Koslucher et al., 2015; Koslucher et al., 2016; Munafo et al., 2017).

The standing balance data recorded herein for the aggressive MS stimulus suggests that MS may disturb the vestibular system. This presumed effect of the MS stimulus on the vestibular system and subsequent standing balance is also supported by prior literature (Basta et al., 2005; Carpenter et al., 2001; Nishiike et al., 2013; Yasuda et al., 1999), though these findings relate to standing postures only. Through the lens of traditional posturography literature (Horak, 1991), standing balance is a function of information derived from visual, somatosensory, and vestibular sensory influences. For the EO standing balance condition, subjects could rely on visual, proprioceptive, and vestibular sensory inputs; however, for the ECF standing balance condition, visual sensory information was eliminated (i.e., eyes were closed) and proprioceptive sensory information was diminished (i.e., standing on foam). In context of the results presented herein, sway area was unchanged during the EO condition, as subjects could rely on visual proprioceptive information to maintain balance, even if vestibular afferents were diminished by the MS stimulus. In contrast, sway area was increased significantly following the ECF condition because sensory information from visual, proprioceptive, and vestibular afferents were all either eliminated or diminished. Moreover, subjects also perceived that they were swaying more following the aggressive stimulus (PSPSI) but were unable to correct for the sway they perceived.

Interestingly, however, the effect of the MS stimulus on sway area differed between the mild and aggressive protocols. Whereas the MS stimulus led to an increase in sway area as mentioned above, the mild MS stimulus led to a decrease in sway area. There are a few potential explanations for this observed effect. First, it is important to place these results in context of exposure duration. Unlike the aggressive MS stimulus where all subjects expressed that they were feeling motion sick, seven of the twelve subjects exposed to the mild MS stimulus made it through the entire 30 min of the mild MS stimulus without expressing stomach awareness consistent with the stopping criteria. Therefore, these individuals may not yet have been motion sick to the point where

significant disruption to sensory (i.e., vestibular) information was observed, and the observed reduction in sway area may have arisen from a temporary stress response associated with the mild MS stimulus. Increases in alertness and activation in the dorsolateral prefrontal cortex of the brain have been noted previously to be involved in obtaining attentional resources to maintain upright static balance (Mihara et al., 2008).

The interpretation of these same results, however, through the lens of the postural stability theory of motion sickness may offer an alternative explanation. This is not the first instance in which reductions in spatial magnitudes have been observed after exposure to a MS stimulus, as Stoffregen et al. (2008) and Weech et al. (2018) observed reduced spatial magnitudes following instances of cybersickness. Collectively, these results challenge the traditional assumption that more sway is associated with less postural stability (Stoffregen et al., 2008). In contrast, it is also possible that adopting an overly rigid posture might leave individuals ill-equipped to respond to changing conditions like external perturbations, whereas increased postural sway could demonstrate a better-equipped readiness to respond (Weech et al., 2018). When viewed from this perspective, it is possible that the reduced body sway observed for the mild MS stimulus demonstrates an ineffective postural control strategy that could serve as a precursor to motion sickness, consistent with the postural instability theory of motion sickness presented by Riccio and Stoffregen (1991). To discover which mechanism is indeed responsible for the changes observed herein, future study may benefit from evaluating not only spatial but also temporal dynamics of standing balance prior to and after exposure to a MS stimulus since stability in posture may be defined by more than just movement magnitude (Curry et al., 2020).

A prevailing view of the etiology of low back disorders relates to the load on the spinal tissue relative to the spinal tissue's corresponding tissue tolerance. As muscles are primary loaders of the spinal tissues, changes to neuromuscular recruitment patterns (i.e., muscle coactivity) may serve as the primary mechanism by which a low back injury would occur. It was initially hypothesized that disturbances in the vestibular system consistent with MS would lead to increased muscle coactivity and increased spinal loading. It was also hypothesized that the MS stimulus would yield decreases to low back functional performance because with increased muscle coactivity comes increased “guarding” behavior, thereby reducing trunk velocity, acceleration (Marras et al., 2005). The clinical lumbar motion monitor was able to detect changes in low back function following the mild MS stimulus, thus providing at least one quantitative link between MS and LBDs. However, increases in spinal loading were not ultimately observed for the tasks performed. It should be noted, though, that this observed result may simply be an effect of the simplicity and relative ease of the lifting task chosen. The lifting task was designed to minimize risk of injury following MS exposure. Coactivity is likely to play a larger role in lifting exertions that result in higher external moments being placed on the spine (Marras et al., 2001) or more complex muscle coordination. A more physically demanding or complex lifting task may yield spinal loading changes due to increased coactivity and should be considered for future study.

Relative to the genetic results, levels of circulating miRNA and other small RNAs are known to respond to a tremendous variety of stimuli. These RNAs are thought to be packaged specifically into extracellular vesicles or released directly into circulation. In this study, all circulating RNA was captured and quantified. The levels of each RNA after exposure to mild or aggressive MS stimulus was compared to each subject's baseline prior to stimulus. The time between baseline and post-exposure blood draw was short at approximately 1 h. Therefore, these changes observed here are relatively small in magnitude and represent only the most acute changes in expression. Combined with the small study size, only one miRNA (hsa-miR-3157-3p) had expression changes that remained statistically significant after multiple testing correction using the Benjamini-Hochberg method. It was reliably low in the post-stimulus samples (Table 5). Little is known from the literature about this particular miRNA, except that it is one of the few miRNA that can discriminate schizophrenia patients from healthy controls (Pala and Denkçeken, 2020). Each of the miRNA (or snoRNA) identified in this study should be investigated further in larger studies. Mechanisms for a direct role of each of these remains to be investigated. We hypothesize that these miRNAs may provide insight into the molecular mechanisms associated with the effect(s) of MS on postural stability and LBD.

A single genome-wide association study of motion sickness susceptibility carried out by Hromatka et al. (2015) identified 35 SNPs significantly correlated with motion sickness, which we then genotyped in our study. It should be noted that the Hromatka et al. (2015) study was based on the 23andMe database and that 23andMe relied on web-based questionnaire responses from their participants to determine motion sickness susceptibility. None of the 35 SNPs identified had obvious correlations with our motion sickness variables, although one (rs1378552) had significantly more C alleles in the subjects of the bottom quartile for Pn. No mechanism has been identified for this intragenic SNP. Given the imperfect method used to determine motion sickness susceptibility (i.e., survey), this could be a reason that no dramatic associations were observed. Therefore, another 13 SNPs were chosen for being within genes that control the epigenetic modification of other genes, with minor allele frequencies >15%. We hypothesized that differences in these genes could affect the epigenetic regulation of other genes involved in the motion sickness response. None, however, were found to be different between variables. The phenotypic effect of these SNPs may be individually too small to observe in the small study population used here.

Finally, the results presented herein suggest that standing balance parameters or tests of gene expression may represent viable screening metrics to predict motion sickness and LBD susceptibility in the future. In fact, similar screening tools have already shown promise predicting motion sickness in other populations. For example, the use of pre-exposure temporal sway metrics has previously been shown to predict the intensity of seasickness experienced by maritime novices (Stoffregen et al., 2013). More recently, Weech et al. (2018) showed that sway path length from standing balance can be used alongside other factors like vestibular thresholds, vection magnitudes, and motion sickness susceptibility questionnaire responses to predict cybersickness in a simulated environment.

Of course, the results of this study should also be placed in context with the study's limitations. Namely, this study was performed in a controlled laboratory setting. The investigators implemented some changes between the mild and aggressive protocols, including different equipment and stopping criteria. Additionally, given the number of domains of interest, the results of the MS stimulus in the laboratory may have worn off or diminished in the time between the MS stimulus and some or all of the post- MS exposure biomechanical tests, particularly the biomechanical test(s) near the end of the randomization sequence for each session. Future studies may benefit from assessing biomechanical variables (i.e., kinematics, muscular response) during (rather than or in addition to after) the MS stimulus. This altered timing may be important because motion sickness has consistently been shown to be preceded by instability in the control of seated posture (Chang et al., 2017; Curry et al., 2020; Dong et al., 2011; Merhi et al., 2007; Stoffregen et al., 2000; Stoffregen et al., 2008; Stoffregen et al., 2014; Stoffregen et al., 2017).

During flight and inside the NOTC, military aircrew are/were seated. In contrast, postural stability, gait function, low back function, and lumbar spinal loading data were collected while standing. It is unclear whether the results obtained with stance can be generalized to sitting, though this study is believed to represent a valuable first stop in the investigation of the relationship between MS and LBDs.

There also remain a few limitations surrounding the population chosen to participate in the study. As subject participation was voluntary, it is possible that the subject population was comprised of individuals that are less susceptible to motion sickness as compared to

other peers that would be more susceptible and subsequently self-exclude, which could have diluted the effects of the MS stimulus. Similarly, as all subjects recruited for this study were asymptomatic for LBDs, the results of both MS stimuli may have been diminished relative to those that might be observed in a population with already diminished low back function (i.e., individuals with low back pain). Future studies should assess potential differences in the dependent measures in more susceptible subject populations regarding both LBDs and MS.

5. Conclusion

This study represents an initial attempt to explain an anecdotally observed relationship between motion sickness and low back disorders. Our results provide preliminary evidence that both biomechanical and genetic factors may in fact link both conditions. A MS stimulus altered standing balance, decreased low back function, and led to changes in in the expression of genes with roles in osteogenesis, myogenesis, development of brain lymphatics, inflammation, neuropathic pain, and more.

Author contribution

Here, we highlight the contributions of each of the authors below and will show that each individual has met all of the necessary criteria for authorship by contributing: 1) intellectually (i.e., study design, data collection, and analysis/interpretation of results), 2) in writing or revising the manuscript, and 3) in their final approval of the version that has been submitted.

Jonathan S. Dufour, MS, MBA (Ohio State): participated in all phases of research from study design conception to publication; led coordination among all sites and managed project timelines; collected data on nearly all subjects; developed algorithms and models that processed spinal load data; coordinated data harmonization between sites and compiled data into an official research database; aided in statistical analysis; contributed to all sections of the manuscript; gave final approval of version that has been submitted.

Ali Reiter, PhD (Wright State): coordinated between WPAFB and WSU; transported samples and performed processing of blood specimens to generate cell-free serum and frozen aliquots for analyses; wrote the blood processing protocol. Please note that final approval for the submitted manuscript was impossible, as Dr. Reiter passed unexpectedly during manuscript development. We have also subsequently dedicated the manuscript to her memory in the Acknowledgements.

Cyndy Cox, BS (University of Cincinnati): coordinated and supervised postural stability and gait function team including protocol implementation and setup, training, data collection and analysis; compiled and assisted in interpretation of data; reviewed manuscript; gave final approval of version that has been submitted.

Eric B. Weston, PhD (Ohio State): acquired and processed lumbar spine loading data for several subjects; aided in statistical analysis; wrote the results section; created the figures; provided substantial revisions to the Introduction, Methods, and Discussion sections; formatted the manuscript for final submission; coordinated manuscript revisions across sites; gave final approval of version that has been submitted.

Michael Markey, PhD (Wright State): extracted RNA and DNA from serum and blood specimens; supervised and performed PCR-based genotyping and microarray analysis of circulating small RNAs for all subjects; wrote the Methods, Results, and Discussion surrounding genetics parts of the manuscript; developed Table 3; gave final approval for the submitted manuscript.

Ashley Turner, MEng (University of Cincinnati): collected and processed postural stability and gait function testing on subjects; participated in pilot testing of study equipment, setup and tear-down of equipment at study site; assisted in analyzing and interpreting results; contributed to all sections of the manuscript during initial writing and revision; gave final approval of the version that has been submitted.

Peter Le, PhD (NAMRU-D): participated in study design (motion sickness stimuli, motion sickness surveys); served as NAMRU-D site liaison; collected data on subjects; managed NAMRU-D site data; assisted with Methods section and provided references; provided final approval of version submitted.

Alexander M. Aurand, MS (Ohio State): participated in design of spinal load data collection; set up experimental apparatus for spinal load data; collected data on nearly all subjects; developed algorithms and models that processed spinal load data; aided in statistical analysis; gave final approval of version that has been submitted.

Stacy Simmons, MS (Wright State): for all subjects, processed blood samples for DNA and RNA isolation, quantified the DNA and RNA, genotyped 48 single nucleotide polymorphisms, isolated and purified total circulating small RNAs, and hybridized RNA samples on GeneChips; contributed to the writing of the Methods section; gave final approval of version that has been submitted.

Lorenna Altman, BRST (University of Cincinnati): assisted with protocol development for postural stability and gait function tests; test site set up and tear down; data collection and analysis; compiled and assisted in interpretation of data; gave final approval of version that has been submitted.

Prasath Mageswaran, PhD (Ohio State): aided in securing funding for the project, experimental design conception, coordinated regulatory documentation, data interpretation and contributed to manuscript write up; gave final approval of the version that has been submitted.

Kermit Davis, PhD (University of Cincinnati): involved in the study design, piloting of the data collection, statistical analyses and interpretation of the data results, writing of the manuscript; gave final approval of version that has been submitted.

Dustin Huber, PhD (Navy Medicine Operational Training Center – Pax River): served as principal government liaison, research site manager; oversaw security clearances, Institutional Review Board submissions, revisions and reviews; led subject recruitment and on-site sample processing; gave final approval of the version that has been submitted.

Amit Bhattacharya, PhD (University of Cincinnati): involved in the overall design of the postural stability and dynamic gait assessment strategies with wearable sensors; assisted with data interpretations and the manuscript write up; gave final approval of the version that has been submitted.

William S. Marras, PhD (Ohio State): secured funding for the conceived project; involved in experimental design conception; coordinated data collection, data interpretation, and write up; gave final approval of version that has been submitted.

Declaration of Competing Interest

The study was funded, in part, by the Ohio Federal Research Network, grant number WSARC16-00314. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government. Authors PL and DH are either a military Service member or employee of the U.S. Government. This work was prepared as part of their official duties. Title 17 U.S.C. 105 provides that copyright protection under this title is not available for any work of the U.S. Government. Title 17 U.S.C. 101 defines a U.S. Government work as work prepared by a military service member or employee of the U.S. Government as part of that person's official duties. Approved for public release; distribution is unlimited. The study protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects.

Acknowledgements

This work is dedicated to the memory of Dr. Ali Reiter.

References

Bader, C.E., Giordano, N.A., McDonald, C.C., Meghani, S.H., Polomano, R.C., 2018. Musculoskeletal pain and headache in the active duty military population: an integrative review. Worldviews Evid.-Based Nurs. 15, 264–271.

Basta, D., Todt, I., Scherer, H., Clarke, A., Ernst, A., 2005. Postural control in otolith disorders. Hum. Mov. Sci. 24, 268–279.

Bhattacharya, A., Watts, N.B., Dwivedi, A., Shukla, R., Mani, A., Diab, D., 2016. Combined measures of dynamic bone quality and postural balance–a fracture risk assessment approach in osteoporosis. J. Clin. Densitom. 19, 154–164.

Carpenter, M., Allum, J., Honegger, F., 2001. Vestibular influences on human postural control in combinations of pitch and roll planes reveal differences in spatiotemporal processing. Exp. Brain Res. 140, 95–111.

Catanzariti, J.-F., Guyot, M.-A., Massot, C., Khenioui, H., Agnani, O., Donzé, C., 2016. Evaluation of motion sickness susceptibility by motion sickness susceptibility questionnaire in adolescents with idiopathic scoliosis: a case–control study. Eur. Spine J. 25, 438–443.

Chang, C.H., Chen, F.C., Kung, W.C., Stoffregen, T.A., 2017. Effects of physical driving experience on body movement and motion sickness during virtual driving. Aerosp. Med. Hum. Perform. 88, 985–992.

Chiou, S., Bhattacharya, A., Lai, C.-F., Succop, P.A., 1998. Effects of environmental and task risk factors on workers' perceived sense of postural sway and instability. Occup. Ergon. 1, 81–93.

Cohen, S.P., Nguyen, C., Kapoor, S.G., Anderson-Barnes, V.C., Foster, L., Shields, C., McLean, B., Wichman, T., Plunkett, A., 2009. Back pain during war: an analysis of factors affecting outcome. Arch. Intern. Med. 169, 1916–1923.

Curry, C., Peterson, N., Li, R., Stoffregen, T., Null, N.E., 2020. Postural activity during use of a head-mounted display: sex differences in the "driver–passenger" effect. J. Name Front. Virt. Real. J. 1. Medium: X.

Dai, M., Sofroniou, S., Kunin, M., Raphan, T., Cohen, B., 2010. Motion sickness induced by off-vertical axis rotation (OVAR). Exp. Brain Res. 204, 207–222.

Dobie, T.G., 2019. Motion Sickness: A Motion Adaptation Syndrome. Springer.

Dong, X., Yoshida, K., Stoffregen, T.A., 2011. Control of a virtual vehicle influences postural activity and motion sickness. J. Exp. Psychol. Appl. 17, 128–138.

Dufour, J.S., Marras, W.S., Knapik, G.G., 2013. An EMG-assisted model calibration technique that does not require MVCs. J. Electromyogr. Kinesiol. 23, 608–613.

Ferguson, S.A., Gallagher, S., Marras, W.S., 2003. Validity and reliability of sincerity test for dynamic trunk motions. Disabil. Rehabil. 25, 236–241.

Ferguson, S.A., Marras, W.S., Burr, D.L., Woods, S., Mendel, E., Gupta, P., 2009. Quantification of a meaningful change in low back functional impairment. Spine (Phila Pa 1976) 34, 2060–2065.

Granata, K.P., Marras, W.S., 1995. The influence of trunk muscle coactivity on dynamic spinal loads. Spine (Phila Pa 1976) 20, 913–919.

Harrison, M.F., Coffey, B., Albert, W.J., Fischer, S.L., 2015. Night vision goggle-induced neck pain in military helicopter aircrew: a literature review. Aerospace Med. Hum. Perform. 86, 46–55.

Hartvigsen, J., Hancock, M.J., Kongsted, A., Louw, Q., Ferreira, M.L., Genevay, S., Hoy, D., Karppinen, J., Pransky, G., Sieper, J., Smeets, R.J., Underwood, M., Buchbinder, R., Hartvigsen, J., Cherkin, D., Foster, N.E., Maher, C.G., Underwood, M., van Tulder, M., Anema, J.R., Chou, R., Cohen, S.P., Menezes Costa, L., Croft, P., Ferreira, M., Ferreira, P.H., Fritz, J.M., Genevay, S., Gross, D.P., Hancock, M.J., Hoy, D., Karppinen, J., Koes, B.W., Kongsted, A., Louw, Q., Öberg, B., Peul, W.C., Pransky, G., Schoene, M., Sieper, J., Smeets, R.J., Turner, J.A., Woolf, A., 2018. What low back pain is and why we need to pay attention. Lancet 391, 2356–2367.

Horak, F.B., 1991. Assumptions underlying motor control for neurologic rehabilitation, contemporary management of motor control problems. In: Proceedings of the II STEP Conference. Foundation for Physical Therapy Alexandria, VA, pp. 11–28.

Hromatka, B.S., Tung, J.Y., Kiefer, A.K., Do, C.B., Hinds, D.A., Eriksson, N., 2015. Genetic variants associated with motion sickness point to roles for inner ear development, neurological processes and glucose homeostasis. Hum. Mol. Genet. 24, 2700–2708.

Hutchins Jr., C.W., Kennedy, R.S., 1965. Clinical problems in aviation medicine. Relationship between past history of motion sickness and attrition from flight training. Aerospace Med. 36, 984–987.

Hwang, J., Knapik, G.G., Dufour, J.S., Aurand, A., Best, T.M., Khan, S.N., Mendel, E., Marras, W.S., 2016a. A biologically-assisted curved muscle model of the lumbar spine: model structure. Clin. Biomech. (Brist. Avon) 37, 53–59.

Hwang, J., Knapik, G.G., Dufour, J.S., Best, T.M., Khan, S.N., Mendel, E., Marras, W.S., 2016b. A biologically-assisted curved muscle model of the lumbar spine: model validation. Clin. Biomech. (Brist. Avon) 37, 153–159.

Kim, J., Eom, G.M., Kim, C., Kim, D.-H., Lee, J.-H., Park, B., Hong, J., 2010. Sex differences in the postural sway characteristics of young and elderly subjects during quiet natural standing. Geriatr Gerontol Int 10, 191–198.

Kim, S.H., Lee, S.Y., Kim, J.S., Koo, J.W., 2021. Parameters of off-vertical Axis rotation in unilateral and bilateral Vestibulopathy and their correlation with vestibular evoked myogenic potentials. J. Clin. Med. 10.

Koslucher, F., Haaland, E., Malsch, A., Webeler, J., Stoffregen, T.A., 2015. Sex differences in the incidence of motion sickness induced by linear visual oscillation. Aerosp. Med. Hum. Perform. 86, 787–793.

Koslucher, F., Haaland, E., Stoffregen, T.A., 2016. Sex differences in visual performance and postural sway precede sex differences in visually induced motion sickness. Exp. Brain Res. 234, 313–322.

Lawson, B.D., McGee, H.A., Castenda, M.A., Golding, J.F., Kass, S.J., McGrath, C.M., 2009. Evaluation of Several Common Antimotion Sickness Medications and Recommendations Concerning their Potential Usefulness during Special Operations. Naval Aerospace Medical Research Lab, Pensacola, FL.

Marras, W.S., 2012. The complex spine: the multidimensional system of causal pathways for low-back disorders. Hum. Factors 54, 881–889.

Marras, W.S., Wongsam, P.E., 1986. Flexibility and velocity of the normal and impaired lumbar spine. Arch. Phys. Med. Rehabil. 67, 213–217.

Marras, W.S., Parnianpour, M., Kim, J., 1994. A normal database of dynamic trunk motion characteristics during repetitive trunk flexion and extension as a function of task asymmetry, age and gender. IEEE Trans. Rehab. Eng. 2, 137–146.

Marras, W.S., Parnianpour, M., Ferguson, S.A., Kim, J.Y., Crowell, R.R., Bose, S., Simon, S.R., 1995. The classification of anatomic- and symptom-based low back disorders using motion measure models. Spine (Phila Pa 1976) 20, 2531–2546.

Marras, W.S., Ferguson, S.A., Gupta, P., Bose, S., Parnianpour, M., Kim, J.Y., Crowell, R. R., 1999. The quantification of low back disorder using motion measures. Methodol. Validat. Spine (Phila Pa 1976) 24, 2091–2100.

Marras, W.S., Lewis, K.E., Ferguson, S.A., Parnianpour, M., 2000. Impairment magnification during dynamic trunk motions. Spine (Phila Pa 1976) 25, 587–595.

Marras, W.S., Davis, K.G., Ferguson, S.A., Lucas, B.R., Gupta, P., 2001. Spine loading characteristics of patients with low back pain compared with asymptomatic individuals. Spine (Phila Pa 1976) 26, 2566–2574.

Marras, W.S., Ferguson, S.A., Burr, D., Davis, K.G., Gupta, P., 2005. Functional impairment as a predictor of spine loading. Spine (Phila Pa 1976) 30, 729–737.

Merhi, O., Faugloire, E., Flanagan, M., Stoffregen, T., 2007. Motion sickness, console video games, and head-mounted displays. Hum. Factors 49, 920–934.

Mihara, M., Miyai, I., Hatakenaka, M., Kubota, K., Sakoda, S., 2008. Role of the prefrontal cortex in human balance control. NeuroImage 43, 329–336.

Mirka, G.A., Marras, W.S., 1993. A stochastic model of trunk muscle coactivation during trunk bending. Spine (Phila Pa 1976) 18, 1396–1409.

Montero-Odasso, M., Muir, S.W., Speechley, M., 2012. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. Arch. Phys. Med. Rehabil. 93, 293–299.

Munafo, J., Diedrick, M., Stoffregen, T.A., 2017. The virtual reality head-mounted display oculus rift induces motion sickness and is sexist in its effects. Exp. Brain Res. 235, 889–901.

Nishiike, S., Okazaki, S., Watanabe, H., Akizuki, H., Imai, T., Uno, A., Kitahara, T., Horii, A., Takeda, N., Inohara, H., 2013. The effect of visual-vestibulosomatosensory conflict induced by virtual reality on postural stability in humans. J. Med. Investig. 60, 236–239.

NRC, 2001. Musculoskeletal Disorders and the Workplace: Low Back and Upper Extremities, Washington, DC.

Orsello, C.A., Phillips, A.S., Rice, G.M., 2013. Height and in-flight low Back pain association among military helicopter pilots. Aviat. Space Environ. Med. 84, 32–37.

Pala, E., Denkçeken, T., 2020. Evaluation of miRNA expression profiles in schizophrenia using principal-component analysis-based unsupervised feature extraction method. J. Comput. Biol. 27 (8), 1253–1263.

Reason, J.T., Brand, J.J., 1975. Motion Sickness. Academic Press, Oxford, England.

Revilla, F., Larsh, T., Mani, A., Duker, A., Cox, C., Succop, P., Gartner, M., Jarrin Tejada, C., Bhattacharya, A., 2013. Effect of dopaminergic medication on postural sway in advanced Parkinson's Disease. Front. Neurol. 4.

Riccio, G., Stoffregen, T., 1991. An ecological theory of motion sickness and postural instability. Ecol. Psychol. 3, 195–240.

Simmons, R., Phillips, J., Lojewski, R., Lawson, B., 2008. A Comparison of Intranasal and Oral Scopolamine for Motion Sickness Prevention in Military Personnel. Naval Aerospace Medical Research Lab, Pensacola, FL.

Stoffregen, T.A., Hettinger, L.J., Haas, M.W., Roe, M.M., Smart, L.J., 2000. Postural instability and motion sickness in a fixed-based flight simulator. Hum. Factors 42, 458–469.

Stoffregen, T.A., Faugloire, E., Yoshida, K., Flanagan, M.B., Merhi, O., 2008. Motion sickness and postural sway in console video games. Hum. Factors 50, 322–331.

Stoffregen, T.A., Chen, F.-C., Varlet, M., Alcantara, C., Bardy, B.G., 2013. Getting your sea legs. PLoS One 8, e66949.

Stoffregen, T.A., Chen, Y.C., Koslucher, F.C., 2014. Motion control, motion sickness, and the postural dynamics of mobile devices. Exp. Brain Res. 232, 1389–1397.

Stoffregen, T.A., Chang, C.-H., Chen, F.-C., Zeng, W.-J., 2017. Effects of decades of physical driving on body movement and motion sickness during virtual driving. PLoS One 12, e0187120.

Warwick-Evans, L.A., Symons, N., Fitch, T., Burrows, L., 1998. Evaluating sensory conflict and postural instability. Theories of motion sickness. Brain Res. Bull. 47, 465–469.

Weech, S., Varghese, J.P., Barnett-Cowan, M., 2018. Estimating the sensorimotor components of cybersickness. J. Neurophysiol. 120, 2201–2217.

Wertheim, A.H., 1998. Working in a moving environment. Ergonomics 41, 1845–1858.

Yasuda, T., Nakagawa, T., Inoue, H., Iwamoto, M., Inokuchi, A., 1999. The role of the labyrinth, proprioception and plantar mechanosensors in the maintenance of an upright posture. Eur. Arch. Otorhinolaryngol. 256, S27–S32.

Zampieri, C., Salarian, A., Carlson-Kuhta, P., Aminian, K., Nutt, J.G., Horak, F.B., 2010. The instrumented timed up and go test: potential outcome measure for disease modifying therapies in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 81, 171.

Zampieri, C., Salarian, A., Carlson-Kuhta, P., Nutt, J.G., Horak, F.B., 2011. Assessing mobility at home in people with early Parkinson's disease using an instrumented timed up and go test. Parkinsonism Relat. Disord. 17, 277–280.