USE OF NEAR-INFRARED SPECTROSCOPY TO EXAMINE CEREBRAL ACTIVATION DURING OPTIC FLOW

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Background: Individuals with visual vertigo describe symptoms of dizziness, disorientation, and/or impaired balance in environments with conflicting visual and vestibular information or complex visual stimuli. Physical therapists often prescribe habituation exercises using optic flow as part of a rehabilitation regimen to treat these symptoms, but there are no evidence-based guidelines for delivering optic flow. While beneficial and often prescribed, it is unclear how the brain processes the visual stimuli.

Objective: The purposes of this study were to use functional near-infrared spectroscopy (fNIRS) to explore cerebral activation during varying types of optic flow and support surfaces.

Design: Cross-sectional

Methods: Fifteen healthy participants stood on a force plate in a virtual reality environment and viewed two types of yaw optic flow (pseudo-random and constant velocity) with or without the presence of a fixation cross while standing on a fixed surface. Thirty participants (15 patients with visual vertigo and 15 age- and gender-matched healthy controls) stood on a force plate in a virtual reality environment and viewed two types of anterior-posterior optic flow (single sine and sum of sines) while standing on a fixed or sway-referenced surface. Changes in cerebral activation were recorded from the bilateral fronto-temporo-parietal and occipital lobes using fNIRS.

Results: Cerebral activation, indicated by a change in oxyhemoglobin concentration, was greater in the bilateral fronto-temporal-parietal lobes when optic flow moving unidirectionally in the yaw plane was viewed with a fixation cross. Cerebral activation was reduced in patients compared to controls in the bilateral anterior fronto-temporal regions during optic flow when

standing on a fixed floor. Cerebral activation was also reduced in patients compared to controls in the right anterior fronto-temporal region during optic flow when standing on a sway-referenced floor.

Conclusions: Greater cortical activation in the bilateral anterior fronto-temporal lobes of healthy adults provides preliminary support for the use of a fixation cross during habituation to optic flow. Patients with visual vertigo show less cerebral activation in regions associated with multi-sensory integration in comparison to healthy controls. This decreased activation may represent an altered ability to perform sensory re-weighting of visual information, leading to symptoms of dizziness and imbalance.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I am incredibly grateful to the University of Pittsburgh for opening wide their doors to higher education for the past three years. The faculty and staff in the School of Health and Rehabilitation Sciences provided didactic experiences that were not limited to the classroom, but included lectures, labs, journal clubs, and conferences. These enriching experiences have given me a wealth of knowledge on which to base my career in teaching and research.

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A list of abbreviations is provided here for the reader:

ANOVA	analysis of variance
AIC	Akaike's Information Criterion
BIC	Schwartz's Bayesian Information Criterion
$CMRO_2$	cerebral metabolic rate of oxygen
COM	center of mass
COP	center of pressure
DHI	Dizziness Handicap Inventory
EEG	electroencephalography
EOG	electrooculography
fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
Hb	deoxyhemoglobin
HbO_2	oxyhemoglobin
ICC	Intraclass Correlation Coefficient
ICF	International Classification of Functioning, Disability and Health
MEG	magnetoencephalography
MSAQ	Motion Sickness Assessment Questionnaire
MSSQ	Motion Sickness Susceptibility Questionnaire
MST	medial superior temporal
MSTd	dorsal medial superior temporal
MT	middle temporal
NIRS	near-infrared spectroscopy

NPL	normalized path length
OKN	optokinetic nystagmus
PET	positron emission tomography
PIVC	parieto-insular vestibular cortex
PPPD	persistent postural-perceptual dizziness
RMS	root mean square
SSQ	Simulator Sickness Questionnaire
STPa	superior temporal polysensory area
SUD	Subjective Units of Discomfort
TBI	traumatic brain injury
VEMP	vestibular evoked myogenic potentials
VIP	ventral intraparietal
VOR	vestibulo-ocular reflex
VPS	visual posterior sylvian
VVAS	Visual Vertigo Analogue Scale

1.0 INTRODUCTION

Traumatic brain injury (TBI) has been called the signature injury of Operation Iraqi Freedom and Operation Enduring Freedom. Over 22% of soldiers in a single Brigade Combat Team returning from Iraq sustained at least one TBI.(Terrio et al., 2009) While this percentage reflects those TBI that were clinician-confirmed, the true prevalence is likely higher due to underreporting and misdiagnosis. Dizziness was reported by 59.3% of soldiers who sustained a TBI post-injury, with an additional 5.1% complaining of dizziness post-deployment.(Terrio et al., 2009) Patients with complaints of dizziness often report that their symptoms are provoked by busy visual environments or optic flow.(Bronstein, 2004; Maskell, Chiarelli, & Isles, 2007) Visual vertigo describes symptoms of dizziness, disorientation, and/or impaired balance induced by environments with conflicting visual and vestibular information or complex visual stimuli.(Bronstein, 1995) These visually-dependent patients may display increased postural sway with full-field visual motion stimuli(Bronstein, 1995; Rábago & Wilken, 2011) which may place them at greater risk for falling. Disequilibrium with changes in optic flow has been reported in a case study of a service member who sustained a mild TBI.(Rábago & Wilken, 2011)

A clinical practice guideline on vestibular rehabilitation for peripheral vestibular hypofunction prescribes habituation exercises as a treatment approach when busy visual environments exacerbate dizziness.(Hall et al., 2016) These habituation exercises may involve

optokinetic stimuli or virtual reality environments.(Alahmari et al., 2014; Hall et al., 2016; Pavlou, 2010; Pavlou, Lingeswaran, Davies, Gresty, & Bronstein, 2004; Szturm, Ireland, & Lessing-Turner, 1994; Vitte, Sémont, & Berthoz, 1994) Such optokinetic stimuli and virtual reality environments have been shown to decrease visual vertigo symptoms when incorporated into a rehabilitation regimen.(Pavlou, Bronstein, & Davies, 2013; Pavlou et al., 2004) Optokinetic stimuli have also decreased symptoms, swaying, and rocking in patients with Mal de Debarquement.(Dai, Cohen, Smouha, & Cho, 2014) Exposure to optokinetic stimuli has been used in the treatment of service members with TBI.(Rábago & Wilken, 2011) While optokinetic stimuli are often utilized by clinicians, evidence-based stimulus parameters for delivery of optokinetic stimuli are not yet known. A better understanding of cortical processing of optic flow information is a necessary first step in establishing optimal rehabilitation regimens that include habituation exercises. Optimal rehabilitation will hopefully speed recovery and facilitate faster return to duty rates for soldiers with complaints of dizziness and imbalance.

The study of cortical processing of optic flow information was previously limited to neuroimaging techniques that required the patient to lie supine and motionless during image acquisition. These included studies of healthy adults using positron emission tomography (PET)(Becker-Bense et al., 2012; Brandt, Bartenstein, Janek, & Dieterich, 1998; Deutschländer et al., 2002; Deutschländer et al., 2004) and functional magnetic resonance imaging (fMRI).(Dieterich, Bense, Stephan, Yousry, & Brandt, 2003; Dieterich, Bucher, Seelos, & Brandt, 1998; Smith, Wall, Williams, & Singh, 2006; Uesaki & Ashida, 2015) Patients with unilateral vestibular neurectomies were also studied with fMRI.(Deutschländer et al., 2008) Near-infrared spectroscopy (NIRS) has emerged as a neuroimaging modality that allows for upright imaging of the patient during functional tasks such as balance and gait. NIRS allows for

measurement of changes in oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) concentration as a means to quantify cortical activation. Use of NIRS to study optic flow has been limited thus far. Wijeakumar et al. explored cortical activation in the primary visual cortex in response to visual motion stimuli.(Wijeakumar, Shahani, Simpson, & McCulloch, 2013) Their study was not designed to assess cortical activation in the middle temporal region, the area of the brain that responds preferentially to optic flow in humans.(Lappe, 2009) To date, no studies have used NIRS to explore optic flow that induces the perception of self-motion (vection), which is important for the judgement, control and guidance of self-motion.(Palmisano, Allison, Schira, & Barry, 2015) Vection is essential for spatial orientation, locomotion, and navigation. It is also not known if patients with visual vertigo process optic flow information in the same manner as healthy individuals. NIRS may provide a means to explore the cortical processing of optic flow information in visually-dependent patients as they attempt to resolve visual-vestibular conflicts.

This study was performed to better understand the processing of optic flow information and the relationship between optic flow and postural control. Changes in cerebral activation during exposure to a visual stimulus designed to induce vection (optic flow in the yaw plane) was explored in healthy adults during quiet stance. Differences in cerebral activation between healthy adults and patients with visual vertigo complaints during exposure to anterior-posterior optic flow while standing on a fixed or sway-referenced surface was explored. Study of the relationship between optic flow and postural responses during quiet stance was conducted by measuring postural sway.

1.1 THE USE OF NEAR-INFRARED SPECTROSCOPY TO QUANTIFY CHANGES IN CEREBRAL ACTIVATION DURING QUIET STANCE

Near-infrared spectroscopy is a non-invasive functional neuroimaging method that measures changes in oxygenation of the blood. The change in intensity of visible red to near-infrared light (690-900 nm) between sources and detectors that are placed on the scalp is measured.

During imaging, flexible fiber optic cables deliver low levels of light (< 0.4 W/cm^2) to the sources on the scalp. This light diffuses through the tissues to a depth of approximately 5-8 mm in the outer cerebral cortex.(Boas & Dale, 2005) The main absorbing chromophores are HbO_2 at 830 nm and Hb at 690 nm.(Strangman, Franceschini, & Boas, 2003) Light that is not absorbed is detected, and flexible fiber optic cables carry the light back to photon detectors within the NIRS instrument. When regions of the brain are active, there are changes in HbO_2 and Hb concentration that affect the absorption of light at different wavelengths because these chromophores have different absorption coefficients. Changes in hemoglobin, as a measure of cortical activation, are calculated using the modified Beer-Lambert law.(Cope et al., 1988) The arrangement of sources and detectors on the scalp can then be used to approximate the location of cerebral activity.(Boas, Dale, & Franceschini, 2004)

Different neuroimaging methods have been used to study systems contributing to postural control. In particular, imaging of the vestibular cortex has included fMRI, PET, magnetoencephalography (MEG), electroencephalography (EEG), and NIRS. A review of the thalamocortical vestibular system published by Lopez and Blanke (Lopez & Blanke, 2011) includes an excellent visual representation of the vestibular cortex in humans and primates and is reprinted here (Figure 1).

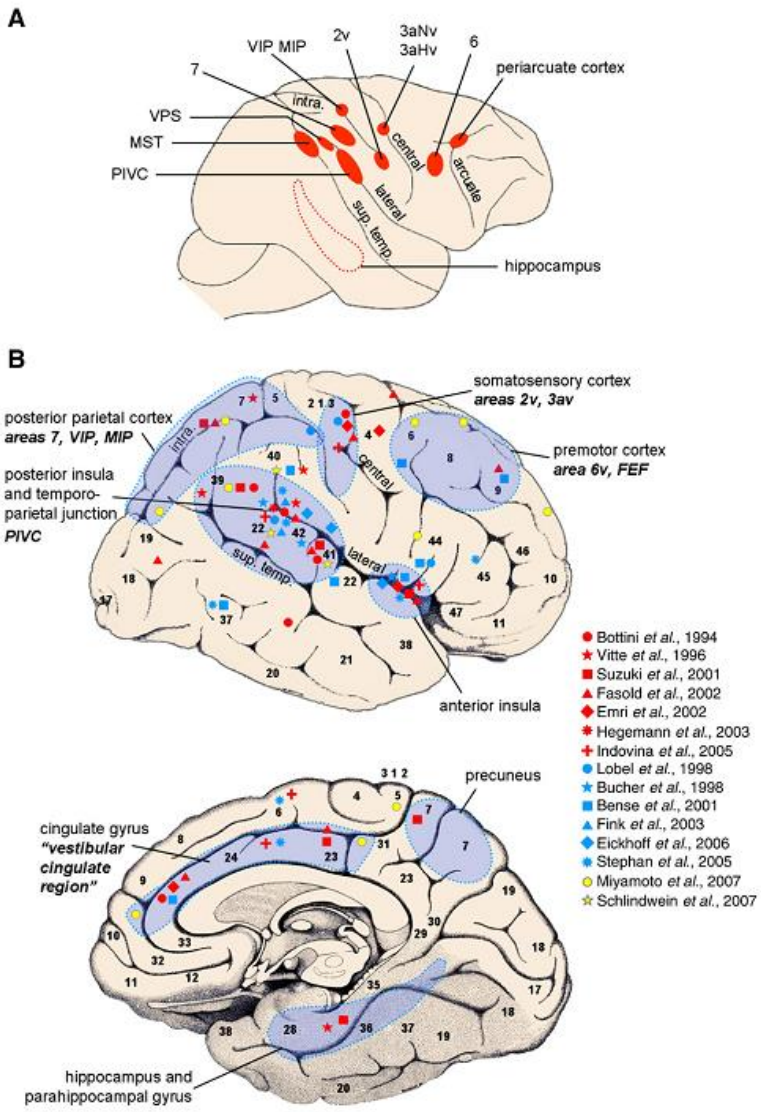


Figure 1. Vestibular cortex in humans and primates. Vestibular areas of the right hemisphere in primates (A) and humans (B), revealed during caloric vestibular stimulation (red), galvanic vestibular stimulation (blue), and brief auditory stimulation (yellow). Bold letters indicate the primate homologue and numbers indicate Brodmann areas. Reprinted from Brain Research Reviews, Volume 67, Christophe Lopez and Olaf Blanke, The thalamocortical vestibular system in animals and humans, Page 129, Copyright 2011, with permission from Elsevier.

Many investigators have explored human postural control, but it has not always been possible to pair assessment of balance with assessment of cerebral activation. Magnetic resonance imaging and PET require subjects to remain in a supine, motionless position during image acquisition. Research conducted in the last two decades has demonstrated that NIRS can be used to measure changes in cerebral activation during a simple balance task (Karim, Schmidt, Dart, Beluk, & Huppert, 2012), during balancing on a balance board,(Herold, Orlowski, Börmel, & Müller, 2017) in response to perturbations (Mihara, Miyai, Hatakenaka, Kubota, & Sakoda, 2008), while walking (Miyai et al., 2001; Mitsuo Suzuki et al., 2004), and while running (Mitsuo Suzuki et al., 2004). Functional NIRS (fNIRS) provides a means to perform neuroimaging under dynamic conditions and a limited number of studies have utilized fNIRS to image the vestibular system.

A benefit of fNIRS compared with other types of neuroimaging (such as MRI and PET) is that subjects are not required to lie in a supine, motionless position during image acquisition. Other benefits of fNIRS are its low cost, small size, and portability. Additionally, it can be combined with MRI and EEG for multimodal neuroimaging.

1.1.1 Problem statement

A recent review stated that vection has been studied using MRI, PET, MEG, and EEG.(Palmisano et al., 2015) To date, no studies have utilized fNIRS to explore cerebral activation during the experience of vection. Cerebral activation has also not been studied in a population with complaints of visual vertigo in comparison to healthy controls using fNIRS. It is not known if the cerebral activation of individuals with complaints of visual vertigo during

exposure to optic flow while standing on a fixed or sway-referenced surface is different than that of healthy individuals.

1.1.2 Purpose

This study was designed to explore changes in cerebral activation and postural responses during optic flow. Two separate experiments were designed to explore these relationships.

In the first study we compared constant velocity and pseudo-random optic flow in the yaw plane in healthy adults. We hypothesized that optic flow that was designed to induce vection would result in increased cerebral activation and postural sway compared to optic flow that was not designed to induce vection.

In the second study we compared patients with complaints of visual vertigo to healthy controls during anterior-posterior optic flow. In all conditions, we hypothesized that patients with complaints of visual vertigo would have greater cerebral activation and postural sway than healthy controls. We also hypothesized that: [1] sum of sines optic flow would result in increased cerebral activation and postural sway compared to single sine optic flow and [2] sway-referencing of the support surface would result in increased cerebral activation and postural sway compared to a fixed support surface. As the sum of sines optic flow was meant to be an unpredictable visual perturbation, we anticipated that it would require increased sensory reweighting (greater cerebral activation) and that it would induce greater postural instability. Additionally, the sway-referenced support surface would provide a greater challenge to the postural control system, so we anticipated that it would require increased sensory reweighting (greater cerebral activation) and that it would induce greater postural instability.

1.2 THE USE OF THE MOTION SICKNESS ASSESSMENT QUESTIONNAIRE AND A THROTTLE DEVICE TO QUANTIFY PERCEPTON OF VECTION DURING OPTIC FLOW IN THE YAW PLANE

The Motion Sickness Assessment Questionnaire (MSAQ) was developed to assess motion sickness as a multidimensional construct.(Gianaros, Muth, Mordkoff, Levine, & Stern, 2001) It has four subscales: gastrointestinal, central, peripheral, and sopite-related.(Gianaros et al., 2001) The subject rates 16 statements on a 1 to 9 scale (1 is "not at all" and 9 is "severely"). The motion sickness score is equivalent to the percentage of total points scored (sum of points from all items/144) × 100.(Gianaros et al., 2001) The subscale scores are equivalent to the percent of points scored within each category (gastrointestinal, central, peripheral, and sopite-related).(Gianaros et al., 2001) The MSAQ has been used as an outcome measure in the published (approximately 30 peer-reviewed journal articles) and unpublished (approximately 4 masters and doctoral dissertations) literature.

The validity of the MSAQ is only described in the original research report by Gianaros et al.(Gianaros et al., 2001) Overall scores from the MSAQ correlated strongly with overall scores from the Pensacola Diagnostic Index ($r = 0.81$, $p < 0.001$) and the Nausea Profile ($r = 0.92$, $p < 0.001$).(Gianaros et al., 2001) The Pensacola Diagnostic Index is a means of grading the severity of acute motion sickness.(Graybiel, Wood, Miller, & Cramer, 1968) The Nausea Profile is a means of capturing the subjective experience of nausea, which can be variable between individuals and circumstances.(Muth, Stern, Thayer, & Koch, 1996) These results led to the authors' conclusion that the MSAQ provides a valid assessment of motion sickness.(Gianaros et al., 2001) Scores from the gastrointestinal subscales of the MSAQ and the Nausea Profile were also correlated ($r = 0.95$, $p < 0.001$).(Gianaros et al., 2001) Scores pertaining to the somatic

distress dimension of the Nausea Profile correlated with the central, peripheral, and sopite-related subscales of the MSAQ ($r = 0.80$, $p < 0.001$; $r = 0.76$, $p < 0.001$; and $r = 0.83$, $p < 0.001$, respectively).

In lieu of an outcome measure such as the MSAQ, other researchers have used devices to capture data on the experience of vection. Previous studies have asked subjects to press a button when they perceive vection, and to keep the button depressed for the duration self-motion is experienced.(Andersen & Braunstein, 1985; Nakamura, 2006; Seno & Nakamura, 2013; Tanahashi, Ujike, Kozawa, & Ukai, 2007) Continuous button presses were used in other studies.(S. Nakamura & Shimojo, 1998; Seno, Ito, & Sunaga, 2009; Seno, Sunaga, & Ito, 2010) During seated vection conditions, subjects have rated the strength of self-motion using a throttle device.(Apthorp, Nagle, & Palmisano, 2014) Similarly, subjects have used a dial to indicate angular velocity and acceleration of self-motion while seated in a flight simulator.(Young, Dichgans, Murphy, & Brandt, 1973)

There is inconsistent use of rating scales for quantifying vection in the published literature. Subjects have rated the frequency of vection on a 4-point scale (0 being "never" and 3 being "always") and the strength of vection on an 11-point scale (0 being "almost not existent" and 10 being "very strong").(Keshavarz & Berti, 2014) Similar scales for vection ranging from 0 to 10 have been used.(Tanahashi et al., 2007; Tarita-Nistor, González, Spigelman, & Steinbach, 2006) Subjects have also rated their vection as a percentage (0% being purely object-motion and 100% being purely self-motion).(Webb & Griffin, 2003) Other studies had subjects rate the strength of vection on a 0 to 100 scale.(Nakamura & Shimojo, 1998; Palmisano, Apthorp, Seno, & Stapley, 2014; Seno et al., 2010) Nakamura et al. used a 0 ("no vection was

perceived") to 100 ("vection of the same strength as that with standard stimulus was perceived") or beyond (i.e., 150 or 200) scale for intensity of vection.(Nakamura, 2006)

1.2.1 Problem statement

As there is no consistent use of rating scales for quantifying vection, and pilot testing revealed that such scales were challenging for subjects to apply, we used item 14 ("I felt like I was spinning") of the MSAQ rated on a 1 to 9 scale as a measure of vection intensity. This did not allow us to measure the latency or duration of vection, however, and so a throttle device was also utilized. The throttle device used by Apthorp et al.(Apthorp et al., 2014) during seated conditions was too cumbersome for use during our standing conditions. A custom throttle device was built using a linear light dimmer switch (Figure 2). It allowed data collection on the intensity, latency, and duration of the perception of vection. It is not known if measures of the perception of vection captured by the MSAQ and throttle device correlate with changes in cerebral activation during quiet stance.

Figure 2. Throttle device. The custom throttle device was built using a linear dimmer switch and allowed data collection on the intensity, latency, and duration of vection.

1.2.2 Purpose

This portion of the study was designed to investigate if changes in cerebral activation are related to the perception of vection during optic flow. Specifically, we investigated the hypothesis that optic flow designed to induce vection would result in increased cerebral activation and increased ratings on item 14 of the MSAQ compared to optic flow not designed to induce vection. Since the brain must process visual information for perception of vection, we anticipated that the constant velocity optic flow would require increased sensory reweighting (greater cerebral activation) and that it would induce greater postural responses in the direction of the visual motion. As the pseudo-random optic flow was not meant to induce vection, we anticipated that it would require decreased sensory reweighting (lesser cerebral activation) and that it would not induce a postural response. As fixation is known to enhance the perception of vection, we anticipated that the viewing optic in the presence of a fixation cross would lead to greater cerebral activation. Finally, we anticipated that the subjects would rate higher self-motion intensity during trials meant to induce vection (constant velocity optic flow).

2.0 BACKGROUND AND SIGNIFICANCE

Visual vertigo is characterized by vertigo, dizziness, or imbalance during situations of intense visual stimulation, such as that encountered when walking down the aisle of a supermarket (Bronstein, 1995). Visual vertigo has shared characteristics with space and motion discomfort(Jacob et al., 1993), phobic postural vertigo(Brandt, 1996), and chronic subjective dizziness(Staab, 2012; Staab & Ruckenstein, 2007). Table 1 illustrates the similarities and differences amongst these disorders. There are several features that make these distinct designations, but based on some overlapping symptom profiles, they have now been enveloped into the diagnosis of persistent postural-perceptual dizziness (PPPD).(Bittar & Lins, 2015) Persistent postural-perceptual dizziness is characterized by dizziness and complaints of persistent swaying or postural instability not detectable during quantitative examination (such as computerized dynamic posturography); symptoms that are worse during head movement, with complex visual stimuli, and when standing; and anxiety.(Bittar & Lins, 2015) In the ICD-11 Beta Draft, PPPD has been included as a chronic vestibular syndrome.("ICD-11 Beta Draft,")

Table 1. Diagnoses for patients complaining of symptom provocation in environments with intense visual stimulation.

Space and Motion Discomfort (Jacob, 1993)	**Visual Vertigo** (Bronstein, 1995)	**Phobic Postural Vertigo** (Brandt, 1996)	**Chronic Subjective Dizziness** (Staab, 2012)	**Persistent Postural-Perceptual Dizziness** (Bittar & Lins, 2015)
- Symptoms due to inadequate visual or somatosensory information for spatial orientation - Avoidance behaviors - Illness (vestibular dysfunction) at onset - Panic disorder	- Highly visually dependent - Symptoms worse with optic flow comprised of complex visual stimuli	- Dizziness and persistent sway/instability not detectable during quantitative examination - Perceptual or social situation provokes symptoms, leading to avoidance behaviors - Fluctuating unsteadiness lasting seconds to minutes or momentary perception of false body perturbations - Illness/ emotional shock at onset - Obsessive-compulsive, labile, mildly depressed affect - Anxiety	- Persistent (greater than or equal to three months), non-spinning vertigo - Increased sensitivity to motion stimuli - Difficulty with precision visual tasks	- Persistent sway/instability not detectable during quantitative examination - Symptoms worse during head movements or with complex visual stimuli - Symptoms worse in standing - Illness/ emotional shock at onset - Concurrent disease leading to the symptoms - Anxiety

The prevalence of visual vertigo was reported to be 4.5% in a sample of 242 consecutive patients presenting for complaints of vertigo or dizziness to a neuro-ophthalmic clinic in Switzerland.(de Haller, Maire, & Borruat, 2004) Phobic postural vertigo is characterized by

dizziness and complaints of persistent swaying or postural instability not detectable during quantitative examination that lasts seconds to minutes, and symptoms provoked by perceptual or social situations, leading to avoidance behaviors and anxiety.(Brandt, 1996) In patients 20 to 50 years old, phobic postural vertigo was the most common form of dizziness, occurring in 22-26% of patients in an outpatient dizziness clinic in Germany.(Strupp et al., 2003)

Patients with vestibular disorders who have visual dependence or an inability to resolve sensory conflict may be more susceptible to experiencing visual vertigo.(Guerraz et al., 2001) Patients with visual vertigo are known to have deficits in subjective visual vertical in the presence of a tilted frame or rotating disk.(Guerraz et al., 2001) Patients with visual vestibular mismatch and visual vertigo complaints also exhibit increased postural sway in the presence of a rotating disk.(Guerraz et al., 2001; Van Ombergen et al., 2016) Visually-dependent patients display increased postural sway with full-field visual motion stimuli.(Bronstein, 1995; Rábago & Wilken, 2011) These deficits in spatial orientation and postural stability may place these patients at increased risk for falls and injuries. While the burden of PPPD is not known, the burden of dizziness/vertigo in a sample of German adults reported that 2% of incident cases involved sick leave, medical care, or impaired activities of daily living.(Neuhauser et al., 2008) Similarly, PPPD could be assumed to lead to lost duty days, increased medical care, activity limitations, participation restrictions, and decreased combat power.

The incidence and prevalence of PPPD in service members has not been reported. The symptom distribution of active duty service members post-blast (n = 81) has been studied.(Hoffer et al., 2010) Acutely (within 72 hours), 4% reported vertigo and 98% reported dizziness.(Hoffer et al., 2010) Sub-acutely (4-30 days post-blast), 47% reported vertigo and 76% reported dizziness.(Hoffer et al., 2010) Similarly, service members with chronic blast injuries

(greater than 30 days post-blast) had complaints of vertigo and dizziness of 36% and 84%, respectively.(Hoffer et al., 2010) In another study of active duty service members post-blast (n = 24; 121 ± 97 days after injury), 11% had an abnormal subjective visual vertical test.(Scherer et al., 2011) Ten symptomatic patients were able to undergo computerized dynamic posturography testing and had a mean composite sensory organization test score of 64.(Scherer et al., 2011) This falls well below the mean composite sensory organization test score of 81 ± 6 (mean ± standard deviation) for the healthy military population.(Roberts, Del Toro, Lambert, & Hoppes, 2016) In veterans with a history of blast exposure and/or mild TBI (n = 31), 83.9% had an abnormal subjective visual vertical test and 52.6% had an abnormal sensory organization test.(Akin & Murnane, 2011) While these clusters of signs and symptoms do not imply a diagnosis of PPPD, it is likely that many of the patients could have some degree of visual vertigo post-injury. Qualitative research exploring triggers of dizziness following TBI included "watching things move."(Maskell et al., 2007) Busy visual environments and environments with moving visual stimuli were commonly reported as provocative.(Maskell et al., 2007)

The pathophysiology underlying complaints of visual vertigo is not well understood. Structural MRI was used to study five patients with visual vertigo in comparison to five healthy controls.(Van Ombergen et al., 2017) Voxel-based morphometry revealed a significant volume decrease in the left inferior occipital lobe and right angular gyrus in the patient group.(Van Ombergen et al., 2017) Diffusion tensor imaging also revealed differences in the white matter tracts. Decreased fractional anisotropy was found in the left inferior fronto-occipital fasciculus (the visuospatial network), which could suggest that patients with visual vertigo misinterpret visual information.(Van Ombergen et al., 2017) Increased fractional anisotropy was found in the left inferior cerebellar peduncle, which the authors interpreted as a possible indication of

inadequate compensation.(Van Ombergen et al., 2017) The description of the patient population was limited to age and gender, so the severity and chronicity of the symptoms reported in the patient group is not known. Dizzy patients with complaints of visual vertigo also have more nonspecific hemispheric white matter abnormalities (hyperintensities) than dizzy patients without complaints of visual vertigo.(Pollak et al., 2015) Structural neuroimaging differences in the cerebral cortex in patients with visual vertigo may also manifest as functional neuroimaging differences, such as changes in cortical activation during optic flow.

It has been proposed that treatment of PPPD should include habituation to optic flow.(Bronstein, 2004; Pavlou et al., 2015; Pavlou et al., 2004) A pilot study (n = 26) on the effectiveness of habituation as part of a vestibular and balance therapy regimen for PPPD reported that a little over half of the patients (n = 14) rated the exercises as beneficial, with greater improvements seen in head and body motion than visual motion sensitivity.(Thompson, Goetting, Staab, & Shepard, 2015) The variability in the response to treatment may be due to the low frequency, intensity, and/or time of the prescribed exercises. Most patients were only seen for one session, and were prescribed an individualized home exercise program. Exercises were to be performed twice daily for 1-2 minutes at least 2-3 days per week. This emphasizes the need for evidence-based parameters for treatment of PPPD using optic flow stimuli. Dose is critical for treatment effectiveness, and physical therapists need sound evidence on which to base decisions for frequency, intensity, and timing of habituation exercises. A better understanding of cortical processing of optic flow information and the relationship between optic flow and balance is necessary before optimal rehabilitation regimens can be instituted. Optimal rehabilitation will hopefully reduce complaints of vertigo, dizziness, or imbalance associated with PPPD and curtail related impairments, activity limitations, and participation restrictions.

2.1 OPTIC FLOW

Optic flow is the continual change of images on the retina that occurs from movement of the visual environment. The change of images on the retina is dependent on the direction of gaze and on the movement of the eyes.(Lappe & Hoffmann, 2000) Optic flow provides important afferent information for control of posture and gait speed, and perception of distances in a moving scene, time-to-contact of a moving object, and path length.(Lappe, 2009) Some types of optic flow can induce a feeling of self-motion (vection).

Specific regions of the human and primate brain are active during processing of optic flow information. In humans, these regions include subcortical nuclei and cortical areas. Subcortical nuclei that respond to visual motion include the: dorsolateral geniculate nucleus, pulvinar, superior colliculus, nucleus of the optic tract, oculomotor nuclei, pontine nuclei, tegmental nuclei, and vestibular nuclei.(Banton & Bertenthal, 1997) Cortical areas that respond to visual motion include the: striate cortex (V1); visual areas 2, 3, and 4; fundus of the superior temporal area; middle temporal (MT) area; medial superior temporal (MST) area; superior temporal polysensory area (STPa); parieto-occipital area; ventral intraparietal (VIP) area; and Brodmann area 7A.(Banton & Bertenthal, 1997)

The MT region (Figure 3) is the area of the brain that responds preferentially to optic flow in humans.(Lappe, 2009) The primary function of the MT/MST complex is detection of visual motion and encoding of optic flow information.(Fasold et al., 2002) In particular, the dorsomedial neurons in the MST area are responsive to optic flow.(Banton & Bertenthal, 1997) The MST also has a role in the optokinetic reflex.(Lappe & Hoffmann, 2000) Portions of the parietal lobe are also selective to optic flow. These areas are the VIP area, Brodmann area 7A, and the fundus of the superior temporal sulcus.(Lappe, 2009)

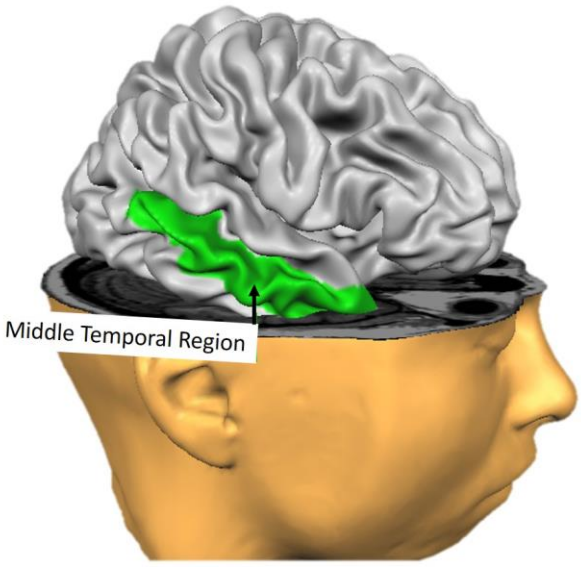


Figure 3. Middle temporal region. The image above was generated using the BrainVoyager tutorial (http://www.brainvoyager.com).

In macaque monkeys, the dorsal medial superior temporal (MSTd) region is responsive to optic flow information.(Chen, DeAngelis, & Angelaki, 2011) However, the parieto-insular vestibular cortex (PIVC) is not responsive to optic flow information.(Chen, DeAngelis, & Angelaki, 2010) Multisensory neurons (responsive to both vestibular and visual stimuli) were found in the visual posterior sylvian (VPS) area, although these had weaker responses to optic flow than the MSTd.(Chen et al., 2011) In rhesus monkeys, the STPa is responsive to optic flow information.(Anderson & Siegel, 1999) Neurons were shown to respond selectively to different types of optic flow (linear, rotary, radial, and spiral), which suggests that the neurons in this region contribute to analysis of the optic flow information.(Anderson & Siegel, 1999)

Knowledge of the anatomical location (and depth) of cortical areas for processing optic flow information is an important consideration for selecting a neuroimaging modality. Imaging with fNIRS is limited to superficial cortical areas with a penetration depth of approximately 5-8 mm in the outer cortex.(Huppert, Franceschini, & Boas, 2009) Therefore, fNIRS could be used to image the striate and extrastriate cortex (visual areas 1, 2, and 4), parieto-occipital area, VIP area, and Brodmann area 7A. Changes of optical signals in these regions during optic flow could then be correlated with changes in balance.

2.1.1 The effect of optic flow on balance

Vection is always accompanied by postural adjustments consisting of head and body movements in the direction of the visual stimulus.(Becker-Bense et al., 2012) When a person is exposed to optic flow, the body sways in the same direction as the visual motion in an attempt to stabilize the body with respect to the visual environment.(Kobayashi, Fushiki, Asai, & Watanabe, 2005) The brain perceives vection in the opposite direction of the visual motion and responds with postural changes to stabilize the body and prevent a fall by swaying in the same direction as the visual motion (countering the perceived vection). A sensory conflict is present, however, because the vestibular and somatosensory systems do not perceive any motion as a result of optic flow. Therefore, the relationship between optic flow and changes in postural sway is not direct.(Apthorp et al., 2014) Visually induced sway increases as a function of the logarithm of the amplitude of the visual stimulus up until the subject falls.(Peterka & Benolken, 1995) This lends support to the idea of a saturation effect, where increasing amplitude (Peterka & Benolken, 1995) or velocity (Lestienne, Soechting, & Berthoz, 1977; van Asten, Gielen, & Denier van der Gon, 1988; van Asten, Gielen, & van der Gon, 1988) of visual field motion causes little to no

additional postural sway. It has been noted in the literature that postural responses occur both with and without perception of vection, further complicating understanding of this relationship.(Palmisano et al., 2015)

The direction of optic flow produces characteristic postural responses, which are discussed in further detail below, beginning with yaw and roll optic flow. The effect of pitch optic flow is then presented, with a brief discussion of the asymmetry of vection perception during these visual stimuli. The effect of linear optic flow is followed by those of expanding, contracting, approaching, and receding optic flow.

2.1.1.1 Yaw optic flow

During yaw optic flow, there is greater anterior-posterior than medial-lateral sway amplitude.(Blanks, Fowler, Zizz, & Williams, 1996) The direction of sway was not as reliable as that observed during linear optic flow, meaning that the subjects did not always sway in the same direction as the visual motion.(Blanks et al., 1996) These conclusions may be influenced by the relatively small sample size (n = 30) and large dispersion of ages of the subjects (range 20-75 years; mean ± SD, 41.3 ± 16.6 years). In contrast to standing balance, a compensatory lateral sway that is greater in the mediolateral direction is seen in sitting balance as a result of yaw optic flow experienced during right and left turns during simulated driver training.(Lee, Yoo, & Jones, 1997)

2.1.1.2 Roll optic flow

During roll optic flow, body sway and tonic tilt occur in the direction of the visual stimulus and vection occurs in the opposite direction.(Dichgans, Mauritz, Allum, & Brandt, 1976) Healthy subjects had an increased lateral sway path and a lateral shift in their center of pressure (COP) in

the direction of the visual stimulus.(Querner, Krafczyk, Dieterich, & Brandt, 2002) Sway path was defined as the total path length traveled by the COP in 1 minute.(Querner et al., 2002) The displacement of the COP occurred several seconds after stimulus onset, and this latency was presumably associated with perception of roll vection.(Querner et al., 2002) After the visual stimulus was stopped, lateral body sway and COP returned to baseline within approximately twenty seconds.(Querner et al., 2002)

Tanahashi et al. found similar results in their study of roll optic flow, reporting that the subject's body leaned in the direction of the visual stimulus.(Tanahashi et al., 2007) While the measure of postural sway was not clearly defined, a study of the methods indicates that the mean distance in the mediolateral and anteroposterior directions was calculated. The average mediolateral movement of the COP during vection conditions was significantly greater than during no-vection conditions.(Tanahashi et al., 2007) The average anteroposterior movement of the COP during vection and no-vection conditions was not significantly different, however.(Tanahashi et al., 2007) It was again found that the deviation in the COP returned to baseline after the visual stimulus stopped. Subjects actually leaned their body, but not their head, slightly past baseline (the initial position prior to onset of visual motion) in the opposite direction after the visual stimulus stopped, but this was not found to be statistically significant.(Tanahashi et al., 2007)

During quiet stance, the lateral shift in COP in response to roll optic flow preceded the experience of vection.(Previc, 1992) For roll optic flow-induced changes, the latency for postural drift and increased sway (oscillations) in the direction of visual motion was about 4.8 seconds.(Previc, 1992) The latency for onset of vection was several seconds longer, at about 7.2 seconds.(Previc, 1992) It was hypothesized that the delay in perception of vection was due to

vestibular afferent information initially indicating the absence of self-motion.(Previc, 1992) The correlation of vection latency and postural drift and oscillations were 0.66-0.73,(Previc, 1992) indicating that there was a strong relationship between vection and balance.

Similar to studies of standing balance during roll optic flow, subjects seated in a cockpit simulator during exposure to roll optic flow in the left and right side windows rolled the cockpit simulator in the direction of the visual stimulus to correct perceived tilt in the opposite direction.(Dichgans, Held, Young, & Brandt, 1972)

2.1.1.3 Pitch optic flow

During upward pitch optic flow the COP is shifted backward and during downward pitch optic flow the COP is shifted forward.(Previc, 1992) During upward pitch optic flow, subjects had posterior movement of their center of mass (COM).(Wang, Kenyon, & Keshner, 2010) In this study, infrared markers were placed on key anatomical landmarks, and a six-camera motion analysis system was used to capture angular displacement of the body segments. Whole body COM was defined as a weighted average of the COM of the body segments.(Wang et al., 2010) The average position of the COM and angular displacement of the head and ankle were measured before and after the visual stimulus. The difference between these two measures was used to calculate the amplitude of the COM. The posterior displacement of the COM increased in amplitude as the velocity of the optic flow increased.(Wang et al., 2010)

The upward pitch optic flow also induced an upward pitch of the head. The magnitude of the angular displacement of the head increased as the velocity of the optic flow increased.(Wang et al., 2010) At 60 degrees per second, the magnitude of the angular displacement of the head was 1.5 degrees and occurred after a 1.2 second latency.(Wang et al., 2010) As the velocity of the optic flow increased, the mean angular displacement of the hip also increased.(Wang et al.,

2010) The subjects' had a slight increase in compensatory hip flexion. Increased ankle dorsiflexion motion was observed in response to all velocities of upward pitch optic flow, but was not significantly different between the levels of velocity of optic flow tested.(Wang et al., 2010)

Kobayashi et al. also measured displacement of the head and body during upward and downward pitch optic flow. The head and body were displaced anteriorly during downward pitch optic flow for the duration of the stimulus.(Kobayashi et al., 2005) The postural responses to upward pitch optic flow, however, were more variable during the stimulus.(Kobayashi et al., 2005) Head displacement was typically larger than displacement of other body segments for both upward and downward pitch optic flow.(Kobayashi et al., 2005) Most subjects moved their head in the same direction as the optic flow to stabilize their head with respect to the visual environment.(Kobayashi et al., 2005) During upward pitch optic flow the head and trunk moved with similar magnitude and phase while the ankles produced smaller magnitude movements that were largely out of phase with the head and trunk.(Keshner & Kenyon, 2000)

Some of the variability over time seen in response to upward pitch optic flow may be attributed to what is known as the up-down asymmetry of vection perception. The up-down asymmetry of vection perception refers to the intensity of vection being perceived as greater during upward than downward optic flow. Mean velocity of induced motion (the illusion of object-motion) was greater for upward than downward optic flow, and this response was velocity dependent (notably at 40 degrees per second).(Lott & Post, 1993) Previc et al. also found that vection was greater for upward than downward pitch optic flow, though the induced postural sway was opposite.(Previc, 1992) The correlation between amplitude of postural sway and intensity of vection was $r = 0.56$ ($p < 0.001$).(Previc, 1992) Pitch optic flow is known to induce

up-down asymmetry during vection and body tilt.(Kobayashi et al., 2005) Downward pitch optic flow had a greater destabilizing effect (increased root mean square) on standing balance than upward pitch optic flow.(Diener, Dichgans, Guschlbauer, & Bacher, 1985) These findings were confirmed by Diener and Dichgans in their later work as well.(Diener & Dichgans, 1988) Asymmetry in postural responses to upward and downward pitch optic flow has been noted, with downward pitch optic flow creating the most postural sway.(Previc, 1992) The greater postural instability induced by downward pitch optic flow (creating the perception of falling backwards) may be due to the biomechanical constraints of the feet and ankles which afford smaller posterior limits of stability.

2.1.1.4 Linear optic flow

Linear optic flow produced a body tilt and rotation of the head and body in the direction of the visual stimulus with slight neck flexion.(Ehrenfried, Guerraz, Thilo, Yardley, & Gresty, 2003) A 0.516 correlation between movement of the visual stimulus and postural sway has been reported.(Stoffregen, 1985) This is similar to the strong, positive correlation between magnitude of vection and postural sway (measured by movement of the head) during linear optic flow (r = 0.74).(Kawakita, Kuno, Miyake, & Watanabe, 2000) Head sway was largest during low frequency (0.01 Hz) and higher velocity optic flow.(Kawakita et al., 2000)

This relationship between frequency of optic flow and magnitude of body sway did not hold true in the study by Kuno et al., however.(Kuno, Kawakita, Kawakami, Miyake, & Watanabe, 1999) The amplitude of postural sway was not dependent on the velocity of the optic flow, though texture was noted to be an influential factor.(van Asten, Gielen, & Denier van der Gon, 1988) Increased postural sway was induced by increased texture (defined as the quantity of

contrast lines within the pattern) of the stimulus.(van Asten, Gielen, & Denier van der Gon, 1988)

Lestienne et al. explored postural sway during linear optic flow and found an initial, fast body sway shortly after the onset of the visual stimulus that slowly returned to a plateau as the individual adapted to the visual stimulus.(Lestienne et al., 1977) The latency of this response was 1.2 ± 0.3 seconds.(Lestienne et al., 1977) During linear optic flow, oscillations in postural sway about this plateau were observed.(Lestienne et al., 1977) After the cessation of the visual stimulus, postural sway in the opposite direction (beyond that seen during the onset) occurred and was variable in duration (50 ± 30 seconds).(Lestienne et al., 1977) The latency of this response was 1.0 ± 0.4 seconds.(Lestienne et al., 1977)

The effect of linear optic flow (conflicting visual-vestibular afferent information) on postural sway was approximately equal to the effect of closing the eyes (absent visual afferent information) on postural sway at frequencies below 0.2 Hz.(Lestienne et al., 1977) Above this frequency, the postural sway produced by closing the eyes was more destabilizing than that produced by the linear optic flow.(Lestienne et al., 1977) Additionally, postural adjustments in the pitch plane lag behind the velocity of the optical stimulus by approximately 30 degrees at low frequencies (approximately 1.7 seconds at 0.05Hz).(Lestienne et al., 1977) With increasing frequencies this phase lag decreased, such that between 0.20 and 0.25 Hz postural adjustments were in-phase with the visual stimulus.(Lestienne et al., 1977) The distance from the optic flow also affects the magnitude of postural sway, with closer objects increasing optic flow thereby increasing visual proprioceptive information and decreasing postural sway.(Lee & Lishman, 1975a)

During linear optic flow, elderly subjects with a history of falls had a longer COP path length than healthy elderly or young subjects.(Haibach, Slobounov, & Newell, 2008) Continuous oscillation of the linear (anteroposterior) optic flow induced larger postural responses than a discrete anterior or posterior motion (visual push) of the stimulus.(Haibach et al., 2008) All subjects swayed in-phase with the stimulus (a virtual moving room), consistent with the findings of other studies.(Haibach, Slobounov, & Newell, 2009; Haibach et al., 2008; Musolino, Loughlin, Sparto, & Redfern, 2006; O'Connor, Loughlin, Redfern, & Sparto, 2008; Prioli, Freitas Júnior, & Barela, 2005; Sparto, Furman, & Redfern, 2006) This sway response is an adaptation to the visual stimulus and the result of sensory integration, with more weight given to visual afferent information to maintain balance. The elderly subjects with a history of falls required 3 seconds longer than the young subjects to regain their stability during discrete anterior motion, while healthy elderly subjects only required 1.5 seconds longer than the young subjects.(Haibach et al., 2008) This was determined as the mean amount of time each group required to regain their postural stability during the two testing conditions (discrete anterior or posterior motion).(Haibach et al., 2008) The subjects were judged to have regained their postural stability when the COP velocity remained below 3 standard deviations from the mean COP velocity.(Haibach et al., 2008)

The young and healthy elderly subjects produced more compensatory movements than the elderly subjects with a history of falls.(Haibach et al., 2008) An inability to change their joint angles at the ankle, knee, and hip may suggest impairments in the "biomechanical constraints" and "postural responses" systems that underlie postural control in these elderly subjects with a history of falls.(Horak, Wrisley, & Frank, 2009) Sedentary elderly swayed more in response to a discrete anterior-posterior movement of a room than active elderly or young

adults, indicating greater difficulty with the presented sensory conflict.(Prioli et al., 2005) A similar sensitivity to optic flow was observed in elderly adults with balance problems, and may be related to a decline in somatosensory function.(Sundermier, Woollacott, Jensen, & Moore, 1996)

More in-phase sway with the stimulus (a moving room) has been reported in motion sick versus non-motion sick (well) subjects.(Stoffregen & Smart, 1998) These motion sick subjects also had a higher gain (defined as the ratio of the magnitudes of anteroposterior postural sway and the visual stimulus) than well subjects during eyes open trials.(Stoffregen & Smart, 1998) This latter finding should be interpreted with caution, however, as there was not a significant difference in gain between the two groups upon repeated testing. Greater lateral sway was observed in the motion sick subjects (mean 1.34 cm) than in the well subjects (mean 0.76 cm) during sum of sines movement of the room.(Stoffregen & Smart, 1998) Using similar methods, another study found no difference in spontaneous postural sway between motion sick and well subjects.(Bonnet, Faugloire, Riley, Bardy, & Stoffregen, 2006) However, motion sick subjects had increased postural sway (displacement of the COP) prior to symptom onset.

Lastly, the periodicity of the linear optic flow affects postural sway. Optic flow that oscillated linearly in a periodic (or predictable) way induced postural responses that were on average four times larger than optic flow that oscillated in a non-periodic (or unpredictable) way.(Musolino et al., 2006) Similarly, continuous oscillation of the linear (anteroposterior) optic flow induced larger postural responses than a discrete anterior or posterior motion (visual push) of the stimulus.(Haibach et al., 2008)

2.1.1.5 Radial optic flow

Apthorp et al. calculated the total sway path as the total distance the COP travelled over 60 seconds.(Apthorp et al., 2014) During radially expanding optic flow, average backward sway was not significantly different from zero because subjects tended to correct their initial backward sway.(Apthorp et al., 2014) During radially contracting optic flow, subjects displayed significantly larger forward sway.(Apthorp et al., 2014) It was hypothesized that this larger magnitude of sway may be due to the fact that the limits of stability are greater in the anterior than posterior direction.(Apthorp et al., 2014) Palmisano et al. reported similar findings; expanding optic flow produced backward sway and contracting optic flow produced forward sway.(Palmisano, Pinniger, Ash, & Steele, 2009) When jitter (shaking) is added to expanding optic flow backward sway is increased, but when jitter is added to contracting optic flow forward sway is decreased.(Palmisano et al., 2009) No significant effects of jitter were seen in the mediolateral direction.(Palmisano et al., 2009) Two previous studies have shown that the intensity of vection can be predicted based on postural sway.(Apthorp et al., 2014; Palmisano et al., 2014) The ratio of postural sway with eyes closed compared with eyes open (the Romberg quotient) was predictive of vection strength in radially expanding optic flow, but not in vertically oscillating radially expanding optic flow.(Palmisano et al., 2014)

2.1.1.6 Location of optic flow

There are conflicting results in the literature about the influence of the location of optic flow on the retina on postural stability. The location of the optic flow, whether central or peripheral, effects postural steadiness. The central area of the visual field has the greatest influence on postural control, with the foveal area particularly contributing to control of lateral sway.(Paulus, Straube, & Brant, 1984) Postural sway was dampened when more than 20% of the central visual

field was occluded compared to a full field of view.(Kawakita et al., 2000) The destabilizing effect of central optic flow was demonstrated by Redfern et al. who noted that central optic flow (viewed monocularly) produced greater amplitude of postural sway in patients with vestibular disorders compared to controls.(Redfern & Furman, 1994) Higher ratings of perceived vection occurred during central optic flow.(Previc, Kenyon, Boer, & Johnson, 1993)

Conversely, Previc et al. found that both postural control and vection are more affected by the peripheral visual field.(Previc et al., 1993) The differences may lie in the structure of the optic flow according to Stoffregen. He proposed that the peripheral retina is unable to detect radial optic flow, while the central retina is able to detect both radial and lamellar (horizontal) optic flow.(Stoffregen, 1986) The work of Andersen and Dyre confirmed that the central retina is able to detect both radial and lamellar optic flow, inducing postural adjustments.(Andersen & Dyre, 1989) Lamellar optic flow was found to induce postural sway, whether central or peripheral, while radial optic flow was found to induce postural sway only when central.(Stoffregen, 1985; Stoffregen, 1986) Warren and Kurtz also found that the peripheral retina is unable to detect radial optic flow, leading to their proposal of the functional sensitivity hypothesis on the role of central and peripheral vision for the perception of vection.(Warren & Kurtz, 1992)

In earlier experiments, Stoffregen found increased postural sway in response to lamellar optic flow in the periphery compared to radial optic flow in the central visual field.(Stoffregen, 1985) The peripheral visual field was more effective in inducing postural sway than the central visual field.(Stoffregen, 1985) Comparing 50% occlusion of the central visual field to the same area of occlusion of the peripheral visual field, postural sway was decreased more with occlusion of the peripheral visual field, lending further support to Stoffregen.(Kawakita et al., 2000)

Stoffregen's work in the structure of optic flow may also explain the findings of van Asten et al., who found different effects when masking the central or peripheral visual field during radial and linear optic flow.(van Asten, Gielen, & Denier van der Gon, 1988)

In addition to the location of optic flow, information relating to depth of the visual field (presented as a radial pattern with or without a graded spatial frequency) affects postural steadiness.(Masson, Mestre, & Pailhous, 1995) Subjects viewing the pattern with a graded spatial frequency demonstrated greater postural stability than those viewing a pattern without depth information.(Masson et al., 1995) Comparing the postural data produced by these two patterns during optic flow, it was concluded that optic flow does not induce postural changes, but instead, regulates postural sway according to spatial and temporal aspects of the visual stimulus.(Masson et al., 1995) The fast Fourier transform amplitude of anteroposterior sway at a particular frequency is largely determined by the frequency of the anteroposterior oscillating movement of the optic flow.(Masson et al., 1995) The relationship of the amplitude of anteroposterior sway at a particular frequency and the temporal frequency of the optic flow is non-linear (inverted U-shape).(Masson et al., 1995)

2.1.1.7 Age and postural sway

Age appears to be a moderating factor in magnitude of postural sway. Haibach et al. exposed three age groups (18-20, 60-69, and 70-79 years) to five conditions of an anteroposterior oscillating virtual moving room while they stood on a force plate measuring movement of their COP.(Haibach et al., 2009) All subjects swayed in-phase with the virtual moving room.(Haibach et al., 2009) The greatest amount of postural sway was observed in the condition where only peripheral vision was stimulated for the 60-69 and 70-79 year olds, likely because the older patients relied on both central and peripheral vision to provide cues to self-motion for the

maintenance of balance.(Haibach et al., 2009) Anteroposterior motion was greater in the older adults in all conditions.(Haibach et al., 2009) The 18-20 year olds often swayed ahead of the virtual moving room, indicating that younger subjects may be better at anticipating the movement of the room than older subjects.(Haibach et al., 2009)

During anteroposterior oscillating optic flow, older adults also had greater head sway velocity than young adults regardless of the amplitude of the visual stimulus.(O'Connor et al., 2008) Additionally, older adults required a greater number of exposures to the visual stimuli before their head sway velocity decreased (a measure of habituation) in comparison to young adults.(O'Connor et al., 2008) This suggests that aging impacts sensory reweighting. In another study of anteroposterior oscillating optic flow, older adults had more head sway in-phase with the visual stimuli than young adults.(Sparto et al., 2006) The ratio of head sway during optic flow to head sway during baseline (no optic flow) trials was two to three times greater in the older adults than the young adults.(Sparto et al., 2006) Blanks et al. also observed greater anteroposterior motion in older adults (60-75 year olds) compared to younger adults (30-45 year olds) during yaw optic flow, as well as greater variability in the older adults' sway.(Blanks et al., 1996)

The effects of an oscillating moving room on the frequency, amplitude, and timing of postural sway was examined in 3-6 year old children.(Schmuckler, 1997) The children swayed in-phase with the moving room.(Schmuckler, 1997) Moving from a faster to a slower velocity of optical flow resulted in greater frequency of sway and maximum cross-correlation values (a measure of "the strength of perception-action coupling" or "visual-motor integration") than moving from a slower to a faster velocity.(Schmuckler, 1997) It was concluded that 3-6 year old children had postural sway similar to that of adults, however, this conflicts with the findings of

another study reporting that postural sway differed between 7-11 year old children and adults.(Baumberger, Isableu, & Flückiger, 2004) These conflicting findings may be due to the different ages of the children or the types of optic flow (moving room versus ground).

Baumberger et al. compared postural stability of children (7-11 years old) and adults (30 ± 10 years old) in response to ground optic flow. Approaching optic flow resulted in posterior displacement of the COP and receding optic flow resulted in anterior displacement of the COP.(Baumberger et al., 2004) Postural latencies were calculated as the time between the onset or offset of motion and the first postural response observed.(Baumberger et al., 2004) Approaching optic flow had shorter sway latencies at the offset of motion compared to the onset of motion.(Baumberger et al., 2004) The onset of approaching optic flow produced greater postural instability and longer sway latencies in children than receding optic flow.(Baumberger et al., 2004) Similarly, infants showed greater postural responses to an approaching than receding wall.(Bertenthal & Bai, 1989) Children that were 7-9 years old had longer sway latencies at the onset of approaching optical flow than adults.(Baumberger et al., 2004) Children that were 7-11 years old had shorter latencies at the offset of approaching optical flow than adults.(Baumberger et al., 2004) Improvements in postural stability and decreased sway latencies were seen with increasing age.(Baumberger et al., 2004)

Another study explored the effect of sinusoidal anterior-posterior optic flow on the RMS of COP in 4-8 year old children.(Casselbrant, Mandel, Sparto, Redfern, & Furman, 2007) A reduction in postural sway during optic flow was seen from ages 5 to 6.(Casselbrant et al., 2007) This may represent a transitional period during maturation, growth affecting height and mass that requires recalibration of afferent information, or myelination of cortical association areas affecting sensory integration.(Casselbrant et al., 2007) Using the same testing protocol, adults

(20-30 years old) displayed less than half as much RMS sway as the 4-8 year old children.(Borger, Whitney, Redfern, & Furman, 1999) This indicates that children are more visually dependent than adults.

The ability of children (7-12 years old) to use visual afferent information for maintenance of balance is frequency dependent.(Sparto et al., 2006) During anterior-posterior optic flow at 0.1 and 0.25 Hz, 7-12 year old children had greater amplitude of COP sway than young adults (21-30 years old).(Sparto et al., 2006) When the platform was sway-referenced, children swayed 1.3 times as much as young adults, indicating they were able to integrate vestibular and/or other somatosensory cues as well as young adults.(Sparto et al., 2006) When the platform was fixed, children swayed 6.3 times as much as young adults, indicating they were unable to resolve the visual-somatosensory conflict.(Sparto et al., 2006) This again indicates that children are more visually dependent than adults.

Ring et al. studied approaching optic flow with elderly subjects standing on firm and foam surfaces.(Ring, Nayak, & Isaacs, 1988) They found that subjects who suffered an injurious fall recently (within the past 2 weeks) or a fall remotely (within the past several months) had significantly more postural sway than those without a history of falls.(Ring et al., 1988)

2.1.1.8 Vestibular disorders and postural sway

Researchers have explored the effects of different types of optic flow on the postural sway of different patient populations. Though anterior-posterior optic flow has not been explored in patients with visual vertigo, patients with visual vertigo are known to have postural reactions that differ from healthy individuals in response to pitch, roll, and medial-lateral optic flow. Patients with visual vertigo had larger head and trunk angular velocities during upward pitch optic flow than healthy controls.(Keshner, Streepey, Dhaher, & Hain, 2007) Similarly, visually sensitive

patients had larger and more delayed head motions during pitch optic flow than healthy controls.(Keshner & Dhaher, 2008) Patients with visual vertigo also had greater postural sway than healthy controls when viewing roll (rotating disk)(Guerraz et al., 2001) or medial-lateral(Bronstein, 1995) optic flow. So while the postural responses of patients with visual vertigo to pitch, roll, and medial-lateral optic flow has been described, the effect of anterior-posterior optic flow has not been explored.

Anterior-posterior optic flow has been explored in patients with space and motion discomfort. Space and motion discomfort is characterized by symptoms due to inadequate visual or somatosensory information for spatial orientation, with avoidance behaviors and panic disorder.(Jacob et al., 1993) Patients with anxiety and space and motion discomfort are known to have postural reactions that differ from healthy individuals in response to optic flow. The patients had greater overall sway, greater sway during oscillating optic flow, and showed a trend towards persistence of greater sway after viewing optic flow.(Jacob, Redfern, & Furman, 1995) Patients with anxiety and space and motion discomfort also have abnormal posturography findings, especially during sway-referencing of the platform (condition four).(Jacob, Redfern, & Furman, 2009) Though accurate visual proprioceptive information is provided by optic flow during condition four, patients with visual vertigo may not be integrating this information correctly or efficiently, leading to increased postural sway.

Anterior-posterior optic flow has been explored in patients with migraine-associated dizziness. During sinusoidal anterior-posterior optic flow, patients with migraine-associated dizziness had greater RMS of the anterior-posterior COP than subjects with migraine but without dizziness or healthy controls.(Furman, Sparto, Soso, & Marcus, 2005) The authors suggest that this increased postural sway is related to hyperexcitability in the brainstem that may be mediated

by monoaminergic pathways.(Furman, Marcus, & Balaban, 2003) Similar to patients with anxiety and space and motion discomfort, patients with migraine-associated dizziness also demonstrated a surface-dependent pattern during posturography testing.(Furman et al., 2005) They displayed increased postural sway during conditions four and six, and to a lesser degree during condition five.(Furman et al., 2005)

A case report of a patient with agoraphobia and complaints of acrophobia (exposure to heights triggered dizziness) reported postural sway measures during exposure to pitch optic flow.(Whitney et al., 2005) The visual stimulus was delivered to the peripheral field of view and the patient stood on a platform that could be fixed, sway-referenced, or driven (pitched up or down in-phase with the visual stimulus).(Whitney et al., 2005) In addition to increases in root mean square (RMS) total sway, the patient displayed large amplitude, high frequency oscillations, especially when the platform was sway-referenced or driven.(Whitney et al., 2005) The oscillations may be due to a stiffening of the body in an effort to limit movement of the COM and increase postural stability.(Whitney et al., 2005) The oscillations were reduced following eight weeks of vestibular physical therapy.

Anterior-posterior optic flow has been explored in older patients with unilateral vestibular hypofunction. There was no difference in the magnitude of head sway, however, between the older adults with unilateral vestibular hypofunction and age-matched controls.(Sparto et al., 2006) The head sway of both groups was similarly in-phase with the visual stimuli.(Sparto et al., 2006) The patients in this study were likely well compensated based on the results of their rotational testing and low dizziness handicap scores.(Sparto et al., 2006)

In summary, optic flow produces postural adjustments of the head and body in the same direction as the motion, whether it is roll, pitch, linear, expanding, contracting, approaching, or

receding optic flow. The latency of the shift in the COP is related to the onset of the perception of vection during roll optic flow.(Querner et al., 2002) This relationship has not been explored with yaw or pitch optic flow. The postural adjustments seen in response to optic flow stop when the visual stimulus is no longer presented. Patients with visual vertigo have greater postural sway in response to pitch, roll, and medial-lateral optic flow. The effect of anterior-posterior optic flow has not been explored.

2.2 VECTION

Vection is the perception of self-motion. The most commonly cited example is that of being stopped at a stoplight and stepping on the brake in response to perceived self-motion rearward when the neighboring vehicle moves forward. Vection is taught to Army helicopter pilots as the "relative-motion illusion."(*Aeromedical Training for Flight Personnel*, 2009) It is described as a visual illusion of "falsely perceived self-motion in relation to the motion of another object."(*Aeromedical Training for Flight Personnel*, 2009) Pilots are cautioned that such an illusion can occur when flying in formation or hovering over water or tall grass.(*Aeromedical Training for Flight Personnel*, 2009) Additionally, vection can occur with brownout (blowing sand) and whiteout (blowing snow) conditions.(Rupert & Kolev, 2008) The term vection is used in this study according to the classic definition of a visual illusion of self-motion perceived by a physically stationary individual.(Palmisano et al., 2015) Vection can also be used to refer to an illusion of self-motion induced by auditory (acoustic surround motion), haptokinetic (tactile motion applied to a large area of the body), arthrokinetic (passive limb rotation), or biomechanical (repeated stepping motion) stimuli.(Palmisano et al., 2015)

The experience of vection is described as occurring after a 5-10 second latency from the start of the visual stimulus.(Young et al., 1973) The perception of vection is opposite the direction of the visual stimulus, and progresses from movement of the visual field to a slowing of the visual field.(Brandt, Dichgans, & Koenig, 1973) When all of the motion is perceived as self-motion, the visual stimulus (vertical black and white stripes) is often perceived as being stationary.(Brandt et al., 1973; Young et al., 1973) This is known as saturated vection. During constant velocity motion of the visual stimulus, the sensation of vection is intermittent, and it persists for 3-5 seconds after the visual stimulus motion has stopped.(Young et al., 1973) Others report that the sensation of vection persists for 8-11 seconds after the visual stimulus motion has stopped.(Brandt et al., 1973) Following the experience of vection, there is an aftereffect of slow vection in the opposite direction that persists for several minutes.(Young et al., 1973)

The experience of vection can be modified by changing the visual-vestibular interaction. A rotational stimulus resulting in vestibular signals opposite the direction of perceived vection reduces that sensation of vection.(Young et al., 1973) Subjects perceived this as sudden onset of visual stimulus motion without any decrement in angular acceleration of self-motion.(Young et al., 1973) A stimulus resulting in vestibular signals in the same direction of perceived vection increases that sensation of vection.(Young et al., 1973)

Additionally, the experience of vection can be influenced by viewing the visual stimulus in central versus peripheral vision or with or without fixation. Parameters of the visual stimulus, such as size of the field of view, velocity of the visual motion, spatial frequency of the visual stimulus, the presence of foreground and background visual information, and the plane of visual motion also affect the experience of vection.

2.2.1 Influence of central and peripheral vision on perception of vection

There is conflicting literature on the influence of central and peripheral vision on perception of vection. Three main theories on the role of central and peripheral vision for the perception of vection have been proposed.(Bardy, Warren, & Kay, 1999) The first is the peripheral dominance hypothesis, which states that peripheral vision is dominant for self-motion while central vision is dominant for object-motion.(Bardy et al., 1999; Brandt et al., 1973) The location of the visual stimulus on the retina is fundamental to this hypothesis.(Bardy et al., 1999) The second is the retinal invariance hypothesis, which states that information in optic flow determines self- versus object-motion and that this information is independent of stimulus eccentricity.(Bardy et al., 1999) Stimulus eccentricity refers to the stimulus position in the visual field. The work of Nakamura and Shimojo found no evidence for the effect of stimulus eccentricity on magnitude or direction of perceived linear vection.(Nakamura & Shimojo, 1998) The third is the functional sensitivity hypothesis, which states that information in optic flow determines self- versus object-motion but that peripheral and central vision are selectivity sensitive to certain types of optic flow.(Bardy et al., 1999; Warren & Kurtz, 1992) Central vision is sensitive to radial, rotary, and lamellar optic flow, while peripheral vision is only sensitive to lamellar optic flow.(Bardy et al., 1999) It should be noted that the literature is inconsistent in defining central and peripheral vision; an appropriate cutoff seems to be 20 degrees.(Warren & Kurtz, 1992)

Some studies found no difference in central or peripheral stimuli in inducing vection.(Nakamura, 2001; Tarita-Nistor et al., 2006) When the size of the stimulus was equal, no difference in the magnitude of vection induced by central or peripheral stimuli was found.(Nakamura & Shimojo, 1998) However, in a later experiment the central area of the subject's visual field was more effective in facilitating vection than the peripheral

area.(Nakamura, 2006) Others have noted that central vision was capable of inducing vection.(Andersen & Braunstein, 1985; Howard & Heckmann, 1989) These studies conflict with the peripheral dominance hypothesis. A synthesis of the relevant literature favors rejection of this hypothesis.(Bardy et al., 1999)

The vection-inducing potential of central and peripheral stimuli can be represented by the product of stimulus size and stimulus speed.(Nakamura, 2001) Interestingly, the effect of the size of the stimulus on vection was the same for central and peripheral vision.(Nakamura & Shimojo, 1998) If a central and peripheral display move in opposite directions, it is the movement in the periphery that determines the vection.(Brandt et al., 1973) This may lend support to the functional sensitivity hypothesis. Regarding direction of visual stimuli viewed monocularly, temporonasal (lateral to medial) motion induced stronger vection than nasotemporal (medial to lateral) motion.(Seno & Sato, 2009) Motion stimulation on the nasal retina induced stronger vection than the temporal retina.(Seno & Sato, 2009) These findings of directional biases are due to subcortical mechanisms, and do not affect conscious perception of vection.(Seno & Sato, 2009) Based on this study, there are two types of vection; vection can be mediated by cortical and subcortical mechanisms.(Seno & Sato, 2009) fNIRS may provide a means to explore vection mediated by cortical mechanisms.

Eyesight does affect the perception of vection. Vection latency is significantly longer for patients with glaucoma, which negatively affects peripheral vision, than those with normal vision.(Tarita-Nistor, Hadavi, Steinbach, Markowitz, & González, 2014) As glaucoma negatively affects peripheral vision (and particularly motion detection), the longer latencies for vection perception lends support to the peripheral dominance hypothesis. Vection latency is significantly shorter for patients with bilateral age-related macular degeneration, which

negatively affects central vision, than those with normal vision.(Tarita-Nistor, González, Markowitz, Lillakas, & Steinbach, 2008) A similar trend is seen in patients with unilateral age-related macular degeneration.(Hiroaki Fushiki, Takata, Nagaki, & Watanabe, 1999) As peripheral vision is spared in macular degeneration, the shorter latencies for vection perception lends support to the peripheral dominance hypothesis. Vection is not affected, however, by low luminance or large refractive error.(Leibowitz, Rodemer, & Dichgans, 1979)

The functional sensitivity hypothesis provides the most accurate explanation for the role of central and peripheral vision for the perception of vection. The work of Bardy et al. indicates that peripheral and central vision are selectivity sensitive to certain types of optic flow.(Bardy et al., 1999) The information in optic flow about size, speed, direction, and depth then contributes to the perception of the visual stimulus as self- or object-motion.

2.2.2 Influence of fixation on perception of vection

Fixation, the act of maintaining gaze on a single point, has been included in the methodology of many studies. Previous studies have presented a fixation cross (cross hair on which to focus) to inhibit eye movements.(Fushiki, Takata, Yasuda, & Watanabe, 2000; Keshavarz & Berti, 2014; Kovács, Raabe, & Greenlee, 2008; Mergner, Schrenk, & Müller, 1989; Nakamura, 2001, 2006; Pretto, Ogier, Bülthoff, & Bresciani, 2009; Tarita-Nistor et al., 2006; Thilo, Kleinschmidt, & Gresty, 2003; Wiest et al., 2001) One study used electrooculography (EOG) to monitor eye movements and reduce them to a minimum.(Keshavarz & Berti, 2014) In a similar manner, Webb et al. used EOG to ensure that eye movements were similar for their two test conditions (single dot versus multiple dots) with regards to tracking the visual stimuli.(Webb & Griffin, 2003)

During fMRI, EOG was used to record the optokinetic nystagmus (OKN) of both eyes.(Dieterich et al., 1998) The stimulus inducing OKN did not induce vection. Fixation suppression of OKN resulted in increased activation in the supplementary eye field and anterior cingulate gyrus, unchanged activation in the visual cortex, decreased activation in most of the ocular motor areas, and suppressed activation in the anterior and posterior insula and the thalamus.(Dieterich et al., 1998) Fushiki et al. used EOG on some (but not all) of their subjects to ensure the visual stimulation was sufficient to produce OKN.(Fushiki et al., 2000) The slow phase velocity was greater for upward than downward stimulation with increasing stimulus velocity.(Fushiki et al., 2000) The directional preponderance in slow phase velocity of vertical OKN may explain the directional asymmetry in pitch circular vection.(Fushiki et al., 2000) The influence of fixation, however, may confound this explanation. There were also two studies that utilized video-oculography, and while they noted changes in nystagmus, they did not relate this to changes in vection perception.(Brandt et al., 1998; Deutschländer et al., 2008)

The best evidence on the influence of fixation on vection perception was conducted by Tarita-Nistor et al. In the presence of a fixation cross, similar vection is induced by central and peripheral stimulation of equal area.(Tarita-Nistor et al., 2006) With no fixation, peripheral stimulation induced greater vection.(Tarita-Nistor et al., 2006) They also found that the presence of a fixation cross enhanced vection induced by central stimulation (decreased latencies and increased duration) but had no effect on vection induced by peripheral stimulation.(Tarita-Nistor et al., 2006) The duration of vection was also longer with fixation.(Tarita-Nistor et al., 2006) Fixation point oscillation enhanced vection during radial optic flow inducing forward linear vection, evidenced by decreased vection latency and increased duration.(Palmisano, Kim, & Freeman, 2012) Decreased vection latency was also found with fixation during yaw and pitch

optic flow.(Fushiki, Takata, & Watanabe, 2000) A synthesis of the relevant literature indicates that fixation enhances the perception of vection. This may be explained by the increased optic flow afforded by suppression of the OKN.(Tarita-Nistor et al., 2006) Suppression of the OKN causes the visual stimuli to repeatedly move across the retina.(Tarita-Nistor et al., 2006) Alternatively, it may be explained by decreased activation in the vestibular cortex.(Dieterich et al., 1998)

There are some discrepancies in the literature regarding the influence of fixation on perception of vection, however, with Stern et al. reporting that fixation decreased ratings of vection.(Stern, Hu, Anderson, Leibowitz, & Koch, 1990) Central fixation also facilitated vection while peripheral fixation inhibited vection in a study by Palmisano and Kim.(Palmisano & Kim, 2009) Additionally, they found that shifting gaze from the center to the periphery increased ratings of vection during radial optic flow.(Palmisano & Kim, 2009) It was hypothesized that the increased retinal slip during saccades (shifting gaze) was responsible for the increased perception of vection.(Palmisano & Kim, 2009) While much of the literature indicates that fixation enhances the perception of vection, the topic remains controversial.

In studies of the VPS and PIVC of macaque monkeys, neural signals were similar between fixation and no fixation conditions when the animals were translated or rotated in darkness.(Chen et al., 2010, 2011) This finding was likely due to afferent vestibular system (otolith) information, and not retinal slip, efferent oculomotor system information from suppression of the vestibulo-ocular reflex, or smooth pursuit-like information.(Chen et al., 2010, 2011) Since the monkeys were translated or rotated in darkness, the brain responses were attributable to afferent vestibular system information and not afferent visual system information (which was absent).

Besides influencing the perception of vection, fixation also has an influence on visually induced motion sickness. Use of a fixation cross during an optokinetic stimulus suppressed OKN and decreased reported motion sickness.(Webb & Griffin, 2002) This supports the eye movement theory for the origin of visually induced motion sickness, in which OKN stimulates the vagal nerve leading to motion sickness.(Keshavarz, Riecke, Hettinger, & Campos, 2015) Fixation, therefore, would decrease OKN with a resulting decrease in vagal nerve stimulation and motion sickness symptoms. Subjects have reported less nausea during upward pitch optic flow with fixation.(Fushiki et al., 2000)

The relationship between visually induced motion sickness and vection is controversial. The perception of vection was not significantly affected by fixation in the study by Webb and Griffin, and there was no correlation between ratings of vection and motion sickness.(Webb & Griffin, 2002) Conversely, Stern et al. observed that fixation decreased ratings of vection and motion sickness.(Stern et al., 1990) Vection alone is not a sufficient prerequisite for visually induced motion sickness, but might be a necessary prerequisite only in the presence of other contributing factors like sensory conflict, postural instability, or eye movements.(Keshavarz et al., 2015)

2.2.3 Factors affecting perception of vection based on stimulus parameters

The four factors affecting vection are the size of the field of view, the velocity of the visual motion, the spatial frequency of the visual stimulus, and the presence of foreground and background visual information.(Hettinger, 2002) Each of these four factors is discussed below.

2.2.3.1 Size of the field of view

Wide fields of view are more effective at inducing vection than narrower fields of view.(Hettinger, 2002) There is a linear relationship between the magnitude of vection and the area of the field of view.(Nakamura & Shimojo, 1998) The magnitude of vection was measured using continuous button presses and a 0 to 100 scale.(Nakamura & Shimojo, 1998) A similar relationship is seen for the amplitude of induced postural sway, which is proportional to the total area of movement of the field of view.(Lestienne et al., 1977)

2.2.3.2 Velocity of the visual motion

Regarding the velocity of the visual motion, subjects perceived greater estimates of self-motion with higher velocity visual motion (40 degrees per second produced larger estimates than 20 or 30 degrees per second).(Boff, Kaufman, & Thomas, 1986) Perceived velocity of vection is linearly related to stimulus velocity up to 90-120 degrees per second, then velocity of vection lags behind stimulus velocity.(Brandt et al., 1973) Velocity of vection was estimated with reference to a standard stimulus given an arbitrary value of 10, and the latency was measured with a stopwatch.(Brandt et al., 1973) At velocities over 90 degrees per second, there are intervals when vection is not experienced.(Boff et al., 1986) Such a high velocity of continuous vection is rarely encountered naturally, so subjects are undecided about the interpretation of such a visual stimulus.(Boff et al., 1986) The correlation between velocity of the visual motion and magnitude of vection was 0.797 ($p < 0.001$).(Kuno et al., 1999) Magnitude of vection was rated on a verbal 0 to 5 scale and using a joystick (forward or backward tilt indicated forward or backward vection, respectively).(Kuno et al., 1999)

2.2.3.3 Spatial frequency of the visual stimulus

The spatial frequency of the visual stimulus is the third factor affecting vection. Vection increases as stimulus spatial frequency increases.(Boff et al., 1986; Tarita-Nistor et al., 2006; Webb & Griffin, 2003) Subjects were asked to press a button when they perceived vection, and to keep the button depressed for the duration self-motion was experienced.(Tarita-Nistor et al., 2006) The linear relationship between the spatial frequency of the visual stimulus and its perceived velocity(Dichgans & Brandt, 1978) likely accounts for the intensification of vection. An example of increasing stimulus spatial frequency is increasing the number of dots (or any other visual stimulus) in the visual field. Increased texture (defined as the quantity of contrast lines within the pattern) of the visual stimulus is also known to induce increased postural sway.(van Asten, Gielen, & Denier van der Gon, 1988)

2.2.3.4 Presence of foreground and background visual information

The presence of foreground and background visual information is the fourth factor affecting vection. Greater magnitude of vection was induced when the visual stimulus was farther away.(Howard & Heckmann, 1989) A lever with positions for no vection, unsaturated vection, and saturated vection to the right or left was used to record the magnitude and duration of vection.(Howard & Heckmann, 1989) Background motion induces more vection than foreground motion.(Fushiki et al., 2000; Howard & Heckmann, 1989; Keshavarz & Berti, 2014; Seno et al., 2009) A static visual stimulus presented behind a moving pattern in the foreground inhibits vection, but a static visual stimulus presented in front of a moving pattern in the background facilitates vection.(Nakamura, 2006) Increasing the size of this static stimulus increases the inhibition or facilitation of vection.(Nakamura, 2006) Continuous button presses and a 0 (“no vection was perceived”) to 100 (“vection of the same strength as that with standard

stimulus was perceived") or beyond (i.e., 150 or 200) scale was used to measure intensity of vection.(Nakamura, 2006) It is the subject's perception of the visual stimulus (moving pattern) as foreground or background motion, inhibited or facilitated by an object's placement in front of or behind the motion, that contributes to the vection intensity. Andersen et al. suggest that perception of the visual stimulus as having depth was important for generating vection using radial optic flow in the central visual field.(Andersen & Braunstein, 1985) The importance of depth was confirmed by Kawakita et al., who observed a reduction in magnitude of postural sway as central vision was occluded and thereby depth perception was decreased.(Kawakita et al., 2000) Greater than 20% of the central vision had to be occluded to decrease vection perception.

2.2.3.5 Other factors affecting perception of vection

Other attributes of the visual stimulus can also affect vection; it is known that the color red inhibits vection when used as the background or as the moving dots.(Seno et al., 2010) Continuous button presses and a 0 to 100 scale was used to measure latency, duration, and intensity of vection.(Seno et al., 2010) Vection can be suppressed when visual noise (static or twinkling dots) are presented on or distal to the flow plane.(Ito & Takano, 2004) Visual noise is equivalent to static patterns in the suppression of vection.(Ito & Takano, 2004) Subjects pressed one mouse button during weak vection and two mouse buttons during strong vection; buttons were not pressed when vection was not perceived.(Ito & Takano, 2004)

2.2.4 Factors affecting perception of vection based on the plane of visual motion

Vection can occur in yaw, roll, and pitch planes. The factors affecting perception of vection based on the plane of visual motion are discussed below. The perception of vection is greatest for roll, pitch, and linear stimulation, in that order.(Previc, 1992)

Circular (yaw) vection is the illusion of self-rotation induced by a rotating visual field.(Boff et al., 1986) The latency and strength of circular vection are dependent on the velocity of the visual motion, spatial and temporal frequency of the visual stimulus, presence of foreground and background visual information, and the size of the field of view.(Hettinger, 2002) Circular vection induced by central and peripheral visual stimuli was dependent on the relative distances of the visual stimuli to the subject, size of the field of view, and type of motion.(Howard & Heckmann, 1989) The type of motion consisted of six conditions: isolated movement of the central or peripheral field of view, opposite movement of the central and peripheral field of view, central movement with stationary peripheral field of view, and peripheral movement with stationary central field of view.(Howard & Heckmann, 1989)

The same factors affecting the latency and strength of yaw vection affect roll vection.(Hettinger, 2002) Increasing the size of the field of view and increasing the rotational velocity increased the sensation of vection from constant tilt to full, 360 degree roll.(Hettinger, 2002) A visual stimulus rotating counterclockwise produced slightly higher reports of vection than a visual stimulus rotating clockwise, though this was observed in a small sample (n = 10).(Brandt et al., 1998)

Pitch vection produces less sensation of displacement and tilt than roll vection.(Hettinger, 2002) The degree of tilt is less for upward pitch than downward pitch conditions.(Young, Oman, & Dichgans, 1975) Increasing the field of view increases pitch vection, however, the mechanism

underlying the results of this stimulus parameter were not described.(Hettinger, 2002) The illusion of pitching down (due to optic flow moving up) is larger than for pitching up (due to optic flow moving down).(Boff et al., 1986)

Linear vection is defined as uniplanar motion (forward/backward, rightward/leftward, or upward/downward).(Deutschländer et al., 2004) Greater intensity of vection was perceived for roll vection than linear vection.(Deutschländer et al., 2004) Vection and body tilt occur in opposite directions, with tilt reaching a steady state after 18 seconds.(Boff et al., 1986) The sensation of body tilt is increased if the head is rolled 90 degrees or inverted (subjects positioned supine with their head leaning backward over the edge of a platform), compared to when the utricular maculae are oriented horizontally.(Young et al., 1975) When tilted or inverted, the utricles are less sensitive and provide less effective information about the orientation of the head in space.(Boff et al., 1986)

2.2.5 Visual stimulus parameters to induce vection

The optic flow stimulus must be specifically designed to induce self-motion if the effects of vection perception are to be measured. Previously published studies explored different aspects of visual stimuli that affect vection. These include: stimulus type (dots versus stripes), color, number of dots, size of dots, dot density, type of motion (e.g., uniplanar, contracting versus expanding, complex), direction of motion (random versus coherent), velocity, and duration of presentation. The selection of the visual stimulus parameters, including those for inducing vection, for our first study exploring yaw optic flow in healthy adults are discussed below.

The baseline condition was a control condition consisting of stationary white dots on a black background. This is consistent with the control condition utilized by Becker-Bense et

al.(Becker-Bense et al., 2012) and Kovacs et al.(Kovács et al., 2008) Regarding the control condition, the difference between eyes open and eyes closed states was taken into consideration. Studies conducted using fMRI in complete darkness found differences in regions of brain activation between eyes open (ocular motor and attentional systems activated) and eyes closed (visual, vestibular, somatosensory, auditory systems, and olfactory and gustatory cortical areas activated) states.(Dieterich, 2007)

The pseudo-random (sum of sines) condition was intended to simulate randomly moving white dots on a black background. This was consistent with the non-vection-inducing condition utilized by previous researchers.(Becker-Bense et al., 2012; Brandt et al., 1998; Kovács et al., 2008) Random motion of dots does not induce vection.(Becker-Bense et al., 2012; Brandt et al., 1998) Three studies utilized random movement of the visual stimulus in their study methods. Becker-Bense et al. did not define their random dot condition, but they stated it did not produce vection in any of their subjects.(Becker-Bense et al., 2012) Individual spheres moved randomly in the coronal plane with the same speed in the study by Kovacs et al.(Kovács et al., 2008) It is not clearly stated what this speed was, but it may be inferred it was an average of 6 degrees per second (the speed used in the coherent motion condition).(Kovács et al., 2008) Brandt et al. utilized a light grey background with a darker grey circle in the center, on which 190 red and black dots were randomly distributed and moved in a random order at 40 degrees per second.(Brandt et al., 1998) They reported that this condition did not produce vection.(Brandt et al., 1998) This could be due to the random motion and/or the red color of the dots.

The coherent motion condition consisted of 720 white dots covering approximately 20 percent of a black background and rotating rightward or leftward at 40 degrees per second. Brandt et al. used this velocity of visual motion.(Brandt et al., 1998) Subjects perceived greater

estimates of self-motion with higher velocity visual motion (40 degrees per second produced larger estimates than 20 or 30 degrees per second).(Boff et al., 1986) Perceived velocity of vection is linearly related to stimulus velocity up to 90 degrees per second, then velocity of vection lags behind stimulus velocity.(Boff et al., 1986; Brandt et al., 1973) At velocities over 90 degrees per second, there are intervals when vection is not experienced.(Boff et al., 1986)

Vection also increases with increasing stimulus size (more dots).(Boff et al., 1986; Tarita-Nistor et al., 2006; Webb & Griffin, 2003) There are linear relationships between stimulus size and the intensity and duration of vection.(Nakamura & Shimojo, 1998) Increasing dot density (from about 150 to 250 dots) was found to increase vection intensity.(Deutschländer et al., 2004) It is difficult to estimate the increase in the area of the visual field that the dots occupied in their study, as the dots increased in size as they moved from the center of expansion in the linear vection condition and were of various sizes in the roll vection condition. Our dot size and density approximated that of Brandt et al. and Deutschländer et al.(Brandt et al., 1998; Deutschländer et al., 2004) While it is not known what color dots facilitate vection, it is known that red inhibits vection when used as the background or as the moving dots.(Seno et al., 2010) Avoiding red, we utilized white dots on a black background.

There was substantial variability in the literature regarding the duration of trials. For studies that utilized MRI and PET, the visual stimuli were often displayed until the scan was complete. Stimulation conditions ranged in length from 20 seconds(Schraa-Tam et al., 2008; Seno & Sato, 2009) to 7 minutes.(Dieterich et al., 1998) Studies that did not desire to produce vection used shorter trials of 2.5-3.5 seconds.(Keshavarz & Berti, 2014) Kovacs et al. used a design consisting of 60 seconds of coherent motion followed by 15 seconds of incoherent motion and then 15 seconds of no motion repeated 30 times during a 45 minute MRI scan.(Kovács et al.,

2008) A block design consisting of 16 blocks of 15 seconds for a total of 4 minutes has been used; either of two types of optic flow were alternated or one type of optic flow was alternated with a blank field.(Smith et al., 2006) Others utilized 12 second blocks of visual motion alternated with a blank field.(Maloney, Watson, & Clifford, 2014) Tanahashi et al. displayed a stationary image for 10 seconds, a moving image for 120 seconds, and then a stationary image was repeated for 60 seconds.(Tanahashi et al., 2007) Wiest et al. displayed 2 seconds of a stable pattern followed by 2 seconds of random rightward or leftward optic flow.(Wiest et al., 2001) In their self-motion condition, the moving pattern was displayed for 10 seconds before it reversed directions.(Wiest et al., 2001) We utilized 1 minute blocks of stationary dots alternated with either of two types of optic flow. The decision to utilize 1 minute blocks was in part due to the variable latency in vection onset. The latency for onset of vection has been reported to range from 5-10 seconds(Young et al., 1973) to upwards of 40 seconds.(Riecke, Schulte-Pelkum, Avraamides, Heyde, & Bülthoff, 2006) Even longer mean latencies (51.5 to 58.7 seconds) have been reported.(Andersen & Braunstein, 1985)

2.2.6 Quantification of the perception of vection

Once the optic flow stimulus has been specifically designed to induce self-motion, the perception of vection needs to be measured. Researchers have used a variety of devices and rating scales to capture data on the experience of vection. Previous studies have asked subjects to press a button when they perceive vection, and to keep the button depressed for the duration self-motion is experienced.(Andersen & Braunstein, 1985; Nakamura, 2006; Seno & Nakamura, 2013; Tanahashi et al., 2007; Tarita-Nistor et al., 2006) Nesti et al. allowed subjects to control the visual stimulus (a panoramic picture of a forest) though use of a button box.(Nesti, Beykirch,

Pretto, & Bülthoff, 2015) The subjects pushed a button to initiate constant velocity motion of the visual stimulus, and then they pushed a button to terminate the visual motion upon perceiving that the stimuli was stationary (all motion was attributed to self-motion).(Nesti et al., 2015) The elapsed time between button pushes permitted the researchers to quantify the length of time required for saturated vection to occur. When all illusory motion is attributed to self-motion, and the visual stimulus appears stationary, it is called saturated vection. Similarly, Seno and Sato had subjects press a button to initiate the visual stimulus.(Seno & Sato, 2009) In the same study, subjects were also asked to keep pressing a button for the duration vection was experienced.(Seno & Sato, 2009)

Continuous button presses were used in other studies.(Nakamura & Shimojo, 1998; Seno et al., 2009; Seno et al., 2010) Ito et al. had subjects press one mouse button during weak vection and two mouse buttons during strong vection; buttons were not pressed when vection was not perceived.(Ito & Takano, 2004) A button has been used to measure the frequency and duration of vection experienced during exposure to optic flow(Smart, Stoffregen, & Bardy, 2002) and even a lever has been used to record linear vection magnitude estimations.(Berthoz, Pavard, & Young, 1975) Howard and Heckmann used a lever with positions for no vection, unsaturated vection, and saturated vection to the right or left to record magnitude and duration of vection.(Howard & Heckmann, 1989) Investigators have paired a 0 to 5 verbal rating of vection magnitude with tilt of a joystick for measuring anterior or posterior vection direction.(Kuno et al., 1999) During seated vection conditions, Apthorp et al. had subjects rate the strength of self-motion using a throttle device.(Apthorp et al., 2014) Similarly, Young et al. had subjects use a dial to indicate angular velocity and acceleration of self-motion while seated in a flight simulator.(Young et al., 1973)

Previous studies have also used rating scales for quantifying vection. Subjects have rated the frequency of vection on a 4-point scale (0 being "never" and 3 being "always") and the strength of vection on an 11-point scale (0 being "almost not existent" and 10 being "very strong").(Keshavarz & Berti, 2014) A similar scale for vection ranging from 0 to 10 (0 being "no sensation of self-motion" and 10 being "compelling sensation of self-motion") has been used.(Tarita-Nistor et al., 2006) In addition to a 0 to 10 scale for magnitude of vection, subjects have been asked to report the quality of vection, though the latter was not discussed in the report.(Kawakita et al., 2000) Other researchers have used a 0 to 10 scale, but allowed subjects to report the perceived strength of vection to one decimal place (i.e., 6.7)(Tanahashi et al., 2007) or also measured the duration of vection in seconds.(Becker-Bense et al., 2012) Subjects have also rated their vection as a percentage (0% being purely object-motion and 100% being purely self-motion).(Webb & Griffin, 2003) Other studies had subjects rate the strength of vection on a 0 to 100 scale.(Nakamura & Shimojo, 1998; Palmisano et al., 2014; Seno et al., 2010) Nakamura et al. used a 0 ("no vection was perceived") to 100 ("vection of the same strength as that with standard stimulus was perceived") or beyond (i.e., 150 or 200) scale for intensity of vection.(Nakamura, 2006)

In summary, vection is the perception of self-motion. The experience of vection can be influenced by viewing the visual stimulus in central versus peripheral vision or with or without fixation. A synthesis of the relevant literature indicates that fixation enhances the perception of vection. Parameters of the visual stimulus, such as size of the field of view, velocity of the visual motion, spatial frequency of the visual stimulus, the presence of foreground and background visual information, and the plane of visual motion also affect the experience of vection. An understanding of how each of these factors affects the perception of vection is

important for selecting and designing a visual stimulus to induce vection. Numerically based verbal rating scales can be complemented with quantitative throttle ratings to quantify vection intensity. The relationship between such ratings and changes in cortical activation measured using fNIRS has not been explored.

2.3 BALANCE

Balance is the ability to maintain a desired posture without falling. Postural control is the ability to integrate afferent visual, vestibular, and somatosensory information into coordinated, purposeful efferent neuromusculoskeletal responses for maintenance of balance. The central nervous system integrates afferent information using the process of sensory reweighting, whereby the relative importance of afferent information is altered based on changing environmental conditions, and coordinates efferent responses.

2.3.1 Measures of postural control

The postural control system is assessed by means that vary from clinical tests such as the modified Clinical Test of Sensory Interaction on Balance(Shumway-Cook & Horak, 1986) to computerized dynamic posturography testing(Nashner, Black, & Wall, 1982). Postural steadiness describes the performance of the postural control system during static, quiet stance.(Prieto, Myklebust, Hoffmann, Lovett, & Myklebust, 1996) A force plate can be used to measure postural steadiness based on COP displacement. The COP is defined as the location of the vertical ground reaction force vector, representing a weighted average of all the pressures

over the force plate on which the subject is standing.(Winter, 1995) This position is defined by anterior-posterior and medial-lateral coordinates. The position of the COP changes as the subject attempts to maintain their balance by adjusting the applied moments to keep their center of gravity within their base of support. Thus, the COP represents changes in motor control of postural muscles. Time-domain distance measures are the most commonly utilized measures of postural steadiness, and estimate either COP displacement or velocity.(Prieto et al., 1996) Two time-domain distance measures that are commonly utilized are the RMS and normalized path length (NPL).

2.3.2 Postural control strategies during quiet stance

Postural control during quiet stance is regulated by the cerebral cortex.(Gatev, Stambolieva, Lalova, & Dimitrov, 2015) Postural control strategies during quiet stance rely on the integration of afferent sensory information and coordinated efferent motor responses that are appropriately timed and modulated. The afferent sensory information is comprised of visual, vestibular, and somatosensory information. The motor responses vary, but are generally grouped into ankle, hip, and stepping strategies. The magnitude of the perturbation and the type of support surface dictates which strategy is used to attempt to maintain postural control.(Jacobson & Shepard, 2008) These strategies are necessary to oppose the torque from the force of gravity that acts on the body when it deviates from neutral, upright stance. If postural control is to be maintained, the body must generate a motor response that counters the torque imposed by the force of gravity. The 150-200 millisecond delay in the generation of the corrective torque observed by Peterka lends support to the idea that the cerebral cortex regulates postural control during quiet

stance and requires time to integrate afferent sensory information and coordinate efferent motor responses.(Peterka, 2002)

2.3.2.1 Visual system

The visual system is comprised of several anatomical parts, briefly discussed here moving peripheral (eyes) to central (visual cortex). The retina is the photosensitive part of the eye, which contains the macula. The macula is the area with the greatest visual acuity, and is used for focal vision. The area surrounding the macula (perimacular retina) is used for peripheral vision.(Nolan, 2012) The retinal ganglion cells can be divided into two major classes – parvocellular (more prevalent near the fovea) and magnocellular (more prevalent in the periphery).(Stephen et al., 2002) Information gathered from the retina travels through the optic nerve, chiasm, and tract to terminate on the ipsilateral lateral geniculate nucleus, pretectal nuclei, tectum, and hypothalamus.(Nolan, 2012) Axons from the lateral geniculate nucleus relay information to the ipsilateral occipital lobe, specifically the lingual and cuneate gyri.(Nolan, 2012) These two gyri form the primary visual cortex (Brodmann area 17) with the function of visual perception.(Nolan, 2012)

Projections from the visual cortex are organized into two distinct pathways, known as the ventral and dorsal streams. The ventral stream, or occipitotemporal pathway, processes information for object identification.(Goodale & Milner, 1992; Kastner & Ungerleider, 2000) The ventral stream processes stimulus duration, in addition to its roles in visual perception, recognition, and memory.(Becker-Bense et al., 2012) It projects from the striate cortex to the inferotemporal cortex.(Goodale & Milner, 1992) Information from parvocellular ganglion cells is relayed via the ventral stream to V1, V2, and the inferotemporal cortex (to include the fusiform gyrus).(Stephen et al., 2002) The dorsal stream, or occipitoparietal pathway, processes

information for spatial relationships.(Kastner & Ungerleider, 2000) Perception of motion, in particular, is associated with the dorsal stream.(Kastner & Ungerleider, 2000) It projects from the striate cortex to the posterior parietal region.(Goodale & Milner, 1992) Information from magnocellular ganglion cells is relayed via the dorsal stream to V1, V2, MT, and the parietal cortex.(Stephen et al., 2002) Using MEG, afferent information in the central and peripheral field of view was found to travel in separate pathways in the dorsal stream.(Stephen et al., 2002) Shorter latencies for the onset of peripheral visual stimuli were noted in the superior lateral occipital gyrus (putative MT) and intraparietal sulcus.(Stephen et al., 2002) This would seem to indicate that peripheral visual stimuli is relayed through fast, direct pathways.(Stephen et al., 2002) Longer activation in the dorsal stream in response to peripheral than central visual stimuli suggests the dorsal stream has a role in monitoring the periphery.(Stephen et al., 2002)

The visual system provides important afferent information for postural control. This afferent information is divided into two types – focal and ambient. Focal vision allows for the detection of the physical characteristics of objects in the environment.(Berencsi, Ishihara, & Imanaka, 2005) This type of vision answers the question, "What is it?"(Wade & Jones, 1997) It is associated with the ventral stream.(Kandel, Schwartz, & Jessell, 2000) Ambient vision allows for the detection of the spatial characteristics of the environment.(Berencsi et al., 2005; Post & Leibowitz, 1986) This type of vision answers the question, "Where is it?"(Wade & Jones, 1997) It is associated with the dorsal stream.(Kandel et al., 2000) With regards to where the visual information falls on the retina, focal vision occurs in central vision while ambient vision occurs in peripheral vision.(Berencsi et al., 2005; Post & Leibowitz, 1986)

Ambient vision is considered more primitive than focal vision because it is more sensitive to low spatial frequencies, insensitive to refractive error and variations in illumination,

and requires a large area of stimulation in the peripheral field of view.(Andersen & Braunstein, 1985; Post & Leibowitz, 1986) Though primitive, ambient vision requires cortical processing similarly to focal vision.(Andersen & Braunstein, 1985) Based on their study findings that radially expanding optic flow in central vision can induce vection, Andersen and Braunstein purported that the parameters of the visual stimulus, not its location, determines whether it processed as focal or ambient.(Andersen & Braunstein, 1985) Peripheral vision is more effective at decreasing postural sway than central vision.(Berencsi et al., 2005) Central vision is inferior to full (central and peripheral) vision or peripheral vision for the maintenance of quiet stance.(Amblard & Carblanc, 1980) Peripheral vision has an important role in detecting movement, which is important for balance.(Amblard & Carblanc, 1980; Previc & Neel, 1995) Peripheral vision is used to detect self-movement (postural sway) in relation to a stable environment.(Dickinson & Leonard, 1967) Though it may not be peripheral vision so much as the ability to see the body and hands within the peripheral vision that is important for balance.(Dickinson & Leonard, 1967) Conversely, Andersen and Dyre found that central vision was capable of inducing postural adjustments for the maintenance of quiet stance.(Andersen & Dyre, 1989) The visual system stabilizes posture predominately at frequencies below 1 Hz.(Dichgans et al., 1976) It is known to provide more sensitive proprioceptive information than the somatosensory system(Lee & Lishman, 1975a, 1975b) and the vestibular system.(Lee & Lishman, 1975a) Importantly, the visual system can contribute to vection during rotation at a constant velocity, while the vestibular system cannot.(Berthoz et al., 1975; Brandt et al., 1973)

2.3.2.2 Vestibular system

The vestibular system is comprised of several anatomical parts, briefly discussed here moving from peripheral (semicircular canals and otoliths) to central (vestibular cortex). Within the

petrous portion of the temporal bone is the bony and membranous labyrinth for detecting acceleration. Three semicircular canals sense angular acceleration. They are enlarged at one end (the ampulla). The ampulla contains the cupula, below which is the crista that contains the kinocilia and stereocilia that respond to deformation of the cupula in response to movement of endolymph within the semicircular canal. The otoliths (utricle and saccule) sense linear acceleration. Kinocilia and stereocilia are contained within a gelatinous material (embedded with otoconia). They are oriented with respect to a central region known as the striola, such that the utricular excitation occurs in response to horizontal linear acceleration or static head tilt and saccular excitation occurs in response to vertical linear acceleration.(Jacobson & Shepard, 2008; Schubert & Minor, 2004) Information gathered from the semicircular canals and otoliths travels through the superior and inferior divisions of the vestibular nerve to bifurcate in the pontomedullary junction.(Jacobson & Shepard, 2008; Schubert & Minor, 2004) The superior division relays information to the superior and medial vestibular nuclei or the cerebellum (uvula, nodulus, flocculus, or fastigial nucleus).(Brodal & Brodal, 1985; Furuya, Kawano, & Shimazu, 1975; Goldberg, 2000; Korte & Mugnaini, 1979) The inferior division relays information to the medial, lateral, or inferior vestibular nuclei.(Naito, Newman, Lee, Beykirch, & Honrubia, 1995) Information is then relayed to the extraocular motor nuclei, spinal cord, flocculus, reticular formation, thalamus, and vestibular cortex.(Brandt et al., 2002; Brodal & Brodal, 1985; Büttner & Henn, 1976; Highstein, Goldberg, Moschovakis, & Fernandez, 1987; Troiani, Petrosini, & Zannoni, 1976)

In the thalamus, vestibular afferent information is received in the ventral posterior lateral nucleus and the nucleus ventralis intermedius.(Lopez & Blanke, 2011) Rotatory vestibular afferent information activates the ventral posterior inferior nucleus.(Lopez & Blanke, 2011)

Rotatory, translation, and even electrical afferent information activates the ventral posterior medial nucleus.(Lopez & Blanke, 2011) Of the intralaminar nuclei, the centromedian, central lateral, and paracentral nuclei are important for vestibular processing and also project to the basal ganglia.(Lopez & Blanke, 2011)

The vestibular cortex is located near the temporoparietal junction and posterior insula, and includes regions receptive to afferent vestibular information (somatosensory cortex, posterior parietal cortex, anterior insula, lateral and medial frontal cortices).(Lopez & Blanke, 2011) Differing neuroimaging methods and modes of vestibular stimulation make the exact location of the human homologue of the monkey PIVC inconclusive.(Lopez & Blanke, 2011) In general, the superior temporal gyrus is the region of interest for cortical processing of vestibular information. While vestibular projections activate the cortex bilaterally, increased activation on the side of hand dominance has been noted.(Bense, 2003; Dieterich et al., 2003)

The vestibular system provides important afferent and efferent information for postural control. Horak identifies four roles of the vestibular system in postural control. First, the vestibular system provides information about head movement and position, sensed by the semicircular canals and otoliths.(Horak, 2007) Second, the vestibular system helps orient the head and body to vertical as a graviceptive system.(Horak, 2007) Third, the vestibular system helps to control the position of the COM though automatic postural responses.(Horak, 2007) Lower motor neurons that innervate extensor muscles in the limbs are influenced by axons of the lateral vestibulospinal tract originating in the lateral vestibular nucleus.(Nolan, 2012) And fourth, the vestibular system helps stabilize the head with respect to the trunk during postural movements.(Horak, 2007)

Besides its role in postural control, the other role of the vestibular system is stabilizing images on the retina during head movements – the vestibulo-ocular reflex (VOR). The VOR results in compensatory eye movements in the opposite direction of head movement. This reflex consists of a three-neuron arc. Afferent information from the semicircular canals is relayed to the ipsilateral vestibular nuclei. For the horizontal semicircular canal, some of these axons decussate and synapse on the contralateral abducens nucleus, while others ascend to the ipsilateral oculomotor nucleus.(Schubert & Minor, 2004) This provides excitatory input to the ipsilateral medial rectus and contralateral lateral rectus muscles. Conversely, the ipsilateral lateral rectus and contralateral medial rectus muscles receive inhibitory input. For the anterior semicircular canal, some of these axons decussate and synapse on the contralateral oculomotor nucleus.(Schubert & Minor, 2004) This provides excitatory input to the contralateral inferior oblique and ipsilateral superior rectus muscles. The contralateral superior rectus and the ipsilateral inferior oblique muscles receive inhibitory input. For the posterior canal, some of these axons decussate and synapse on the contralateral trochlear and oculomotor nuclei.(Schubert & Minor, 2004) This provides excitatory input to the contralateral inferior rectus and the ipsilateral superior oblique. The contralateral superior oblique and the ipsilateral inferior rectus muscles receive inhibitory input. Such compensatory eye movements allow images to remain stable on the fovea during head movements.

2.3.2.3 Somatosensory system

The function of the somatosensory system is to sense and then relay tactile and proprioceptive information from the periphery to the cerebral cortex. The information is relayed through the dorsal column-medial lemniscus pathway. The receptors in the periphery include mechano-receptors in the dermis and periosteum, muscle spindles, and golgi tendon organs.(Nolan, 2012)

The first order neurons carrying afferent information from these receptors travels in the dorsal column of the spinal cord to the medulla, forming the fasciculus gracilis and fasciculus cuneatus.(Nolan, 2012) After crossing at the level of the medulla, second order neurons ascend as the medial lemniscus. They terminate in the ventral posterolateral nucleus of the thalamus. Information is then relayed to the primary sensory cortex (Brodmann area 3, 1, 2) by thalamocortical fibers.(Nolan, 2012) Specifically, the primary sensory cortex is comprised of the postcentral gyrus and posterior paracentral gyrus.(Nolan, 2012)

The somatosensory system provides important afferent information on body position and contact with the support surface for postural control.(Jančová, 2008) The somatosensory system compliments the information provided by the vestibular system (information about movement of the head), by providing information about the position and movement of the body.(Horak, 2007) Information on how segments of the body are aligned to one another and to the support surface is provided by changes sensed in skin, muscles, and tendons.(Horak, 2007) For instance, when the body sways anteriorly during quiet stance the gastrocnemius and soleus muscles perceive a stretch. This information is relayed to the spinal cord prompting a contraction of these muscles via the monosynaptic stretch reflex. Efferent motor responses in the ankle are proceeded by responses in more proximal muscles in the ipsilateral lower extremity indicating that proprioceptive information initiated in the ankle generates responses by ascending muscle synergies for postural control.(Lewis Michael Nashner, 1977) The somatosensory system is known to provide more sensitive proprioceptive information than the vestibular system.(Lee & Lishman, 1975b) The reliability of this information, however, is dependent on the characteristics of the support surface and position of the feet.(Lee & Lishman, 1975a)

2.3.2.4 Central nervous system

The central nervous system integrates afferent information and coordinates efferent responses to maintain postural control. The cerebral cortex influences lower motor neurons through the pyramidal (corticospinal) and extrapyramidal systems.(Jacobson & Shepard, 2008) The basal nuclei influence motor function as part of a feedback loop amongst the cerebral cortex, basal nuclei, and thalamus. Corticostriate, strio-pallidal, pallido-thalamic, and thalamo-cortical projections form this feedback loop. In addition to the basal nuclei, the subthalamic nucleus, substantia nigra, red nucleus, and reticular formation allow for large movements to maintain postural control.(Jacobson & Shepard, 2008) The amplitude and latency of automatic postural responses are modulated through brainstem and subcortical pathways.(Jacobson & Shepard, 2008) Automatic postural responses contribute to postural control by providing a coordinated efferent response to perturbation.

The medial and lateral vestibulospinal and the reticulospinal tracts are also important components of the postural control system. The medial vestibulospinal tract originates in the medial vestibular nucleus and contributes fibers to the medial longitudinal fasciculus. The lateral vestibulospinal tract originates in the lateral vestibular nucleus and carries vestibular and cerebellar information to the lower motor neurons. The lateral vestibular nucleus receives afferent information from the vestibulocochlear nerve, as well as efferent information from the vermis and fastigal nuclei in the cerebellum.(Jacobson & Shepard, 2008) Descending projections from the fastigial nuclei to the vestibular nuclei and reticular formation influence axial and proximal motor control.(Zhang, Wang, & Zhu, 2016) The reticulospinal tract originates from the reticular formation and influences muscle tone. It also facilitates or inhibits volitional movement (pyramidal system) and myotatic reflexes.(Jacobson & Shepard, 2008)

Myotatic reflexes contribute to postural control by maintaining joint stiffness.(Jacobson & Shepard, 2008) Volitional movement contributes to postural control through the execution of learned, purposeful movements.(Jacobson & Shepard, 2008) These purposeful movements can prevent or counteract a loss of balance.

2.3.3 Sensory integration

Sensory integration is the synthesis of afferent information by the central nervous system. Visual, vestibular, and somatosensory information must be accurately combined in order to formulate an appropriate response. With regards to postural stability, an appropriate response is that of coordinated muscle activity to prevent a loss of balance. The exact manner in which sensory integration occurs is not well understood. Though it is known that deficits in sensory integration of afferent visual information can occur in the elderly.(Teasdale, Stelmach, Breunig, & Meeuwsen, 1991)

Tachibana et al. illustrated sensory integration using fNIRS during a video game dancing task. Playing the game required integration of visual, auditory, and somatosensory information into an appropriate motor response.(Tachibana, Noah, Bronner, Ono, & Onozuka, 2011) Increased cerebral activation was seen in the superior parietal lobe, a region involved in multi-sensory integration, and the superior temporal gyrus, a region involved in sensory-motor integration.(Tachibana et al., 2011) Using a similar video game dancing task that required integration of visual and auditory information, increased cerebral activation was found in the middle temporal gyrus and the frontopolar cortex.(Ono et al., 2014) The medial temporal gyrus is a region involved in integrating multi-modal visual and auditory information.(Ono et al., 2014) Karim et al. used fMRI during a simulated balance task and found increased cerebral activation

in the middle and superior temporal gyri, regions involved in multi-sensory and visual-vestibular integration.(Karim et al., 2014)

The complexity of sensory integration has been demonstrated using EEG during quiet stance with accurate and altered visual and vestibular information.(Gatev et al., 2015) The locations of the EEG signals changed as visual and vestibular information was altered. The major purpose of sensory integration is to minimize sensory conflict through sensory reweighting.(Gatev et al., 2015)

2.3.4 Sensory reweighting

Sensory reweighting is a process whereby the central nervous system reassigns the relative importance of afferent information based on changing environmental conditions. During optic flow there can be a sensory conflict between the visual information (suggesting self-motion) and the vestibular information (suggesting the absence of self-motion). When a sensory conflict is presented, sensory reweighting occurs.(Peterka & Loughlin, 2004) This negative feedback system results in decreased reliance on afferent information that is determined to be unreliable.(Peterka & Loughlin, 2004)

The postural responses recorded during roll optic flow by Previc et al. revealed that after approximately 7 seconds vestibular afferent information was given less weight while visual afferent information was given more weight to maintain balance during quiet stance.(Previc, 1992) Young et al. also proposed differential weighting of visual and vestibular information during vection, with greater weight given to the visual information in the absence of vestibular information or when vestibular information is in the same direction as the vection.(Young et al., 1973) Greater weight is given to the vestibular information when vestibular information is in the

opposite direction as the vection, abolishing the vection.(Young et al., 1973) Tactile stimulation applied to the trunk of military pilots has been shown to decrease the perceived velocity of vection.(Rupert & Kolev, 2008) Greater weight given to somatosensory information in the opposite direction as the vection may explain this decrease. The findings of Mahboobin et al. also lend support to the sensory reweighting hypothesis, as they found decreased weighting of visual system information after subjects viewed a randomly moving scene.(Mahboobin, Loughlin, Redfern, & Sparto, 2005)

Healthy subjects exposed to visual and support surface perturbations also increased reliance on vestibular system information.(Peterka, 2002) Subjects with severe bilateral vestibular loss were unable to perform this sensory reweighting.(Peterka, 2002) With degradation of somatosensory information by manipulation of the support surface, subjects seemingly gave greater weight to visual information.(Lee & Lishman, 1975a) Vision decreased postural sway, especially when the visual information provided reliable rather than unreliable afferent information.(Lee & Lishman, 1975a) Vestibular information was inadequate for balance when the somatosensory information was so severely degraded.(Lee & Lishman, 1975a) Model simulations explored by Peterka and Loughlin favored sensory reweighting as an explanation for excessive torque production generated by subjects on a sway-referenced platform.(Peterka & Loughlin, 2004) One possible sensory reweighting strategy they proposed was that subjects increased the weight of the graviceptive system, which provides information on the body's orientation in space, to compensate for the decreased weight of the proprioceptive system.(Peterka & Loughlin, 2004) Soechting and Berthoz studied subjects standing on a cart, which, when moved at the same velocity and direction as the visual surround, produced greater

anterior pitch of the body.(Soechting & Berthoz, 1979) The amplitude of this response was twice as great as the response to isolated motion of the visual surround.

Karim et al. used fNIRS during computerized dynamic posturography and found increased cerebral activation in the temporoparietal regions during tasks that would be associated with increased weighting of vestibular system information.(Karim, Fuhrman, Sparto, Furman, & Huppert, 2013) In particular, they found that the superior temporal gyrus and supramarginal gyrus are involved in sensory reweighting of visual, vestibular, and proprioceptive system information.(Karim et al., 2013) These findings were replicated by another study using fNIRS over the right hemisphere during computerized dynamic posturography.(Takakura, Nishijo, Ishikawa, & Shojaku, 2015) Additionally, they found that the frontal operculum and parietal operculum were also involved in sensory reweighting.(Takakura et al., 2015) The findings of O'Connor et al. indicate that aging affects sensory reweighting. Older adults require exposure to more trials of optic flow in order to habituate to visual system information.(O'Connor et al., 2008)

In summary, balance is the ability to maintain a desired posture without falling. Measures of postural control vary from bedside to computerized balance testing. Postural control strategies rely on the integration of afferent sensory information in the central nervous system and coordinated efferent motor responses that are appropriately timed and modulated. The cerebral cortex plays a role in the integration and reweighting of sensory information for postural control during quiet stance. The exact mechanisms of these central processes is not well understood, though various neuroimaging modalities have begun to explore cortical regions related to balance.

2.4 NEUROIMAGING OF THE CORTICAL REGIONS RELATED TO BALANCE

Different neuroimaging modalities have been used to study cortical regions related to the integration and reweighting of visual, vestibular, and somatosensory afferent information for postural control. In particular, imaging of the vestibular cortex has included fMRI, PET, MEG, EEG, and fNIRS.

fMRI has been used in conjunction with caloric testing to identify the vestibular cortex as the temporoparietal junction and posterior insula.(Fasold et al., 2002) The region activated during caloric testing extended into the anterior insula, precentral gyrus, postcentral gyrus, areas of the parietal lobe, ventrolateral area of the occipital lobe, and the inferior frontal gyrus including the inferior area of the precentral sulcus.(Fasold et al., 2002) A right-sided dominance was noted, regardless of the side of caloric stimulation; all five subjects were right-handed.(Fasold et al., 2002) Similarly, Suzuki et al. observed activation in the insular gyrus, intraparietal sulcus, superior temporal gyrus, hippocampus, cingulate gyrus, and thalamus.(Suzuki et al., 2001) They also noted right-sided dominance in the intraparietal sulcus.(Suzuki et al., 2001) Vitte et al. also found activation in the hippocampus during cold caloric testing.(Vitte et al., 1996) Stimulation of the otoliths during vestibular evoked myogenic potentials (VEMP) produced similar activation as that observed during stimulation of the semicircular canals.(Miyamoto, Fukushima, Takada, de Waele, & Vidal, 2007; Schlindwein et al., 2008) Though bilateral activation of the posterior insular cortex, middle and superior temporal gyri, and inferior parietal cortex was found during VEMP testing, a right-sided dominance was noted in right-handed subjects.(Schlindwein et al., 2008)

Galvanic vestibular stimulation produced similar findings to caloric vestibular stimulation, activating the temporoparietal junction, central sulcus, precentral sulcus, and

intraparietal sulcus.(Lobel, Kleine, Bihan, Leroy-Willig, & Berthoz, 1998) Natural head movements produced similar findings, with activation in the posterior portion of the planum temporale as well as the temporoparietal junction.(Petit & Beauchamp, 2003) In response to galvanic vestibular stimulation, Bense et al. found vestibular activation (anterior insula, paramedian and dorsolateral thalamus, putamen, inferior parietal lobule, precentral and middle frontal gyrus, middle and superior temporal gyrus, and the anterior cingulate gyrus, in addition to the bilateral cerebellar hemispheres), but noted deactivation in the visual cortex.(Sandra Bense, Stephan, Yousry, Brandt, & Dieterich, 2001) This is evidence of an inhibitory vestibular-visual interaction that lends support to sensory re-weighting. The region of cortical activation was not specific for the frequency (0.1-5.0 Hz) of alternating current-galvanic vestibular stimulation.(Stephan et al., 2005)

Eickhoff et al. combined fMRI with galvanic vestibular stimulation and probabilistic cytoarchitectonic maps of the parietal operculum to define the human PIVC.(Eickhoff, Weiss, Amunts, Fink, & Zilles, 2006) They identified the human homologue of the monkey PIVC as a cortical area in the parietal operculum identified as OP2 (Figure 4).(Eickhoff et al., 2006) Similar to these findings of Fasold et al., Eickhoff et al. also noted right-sided dominance, regardless of the side of galvanic vestibular stimulation.(Eickhoff et al., 2006)

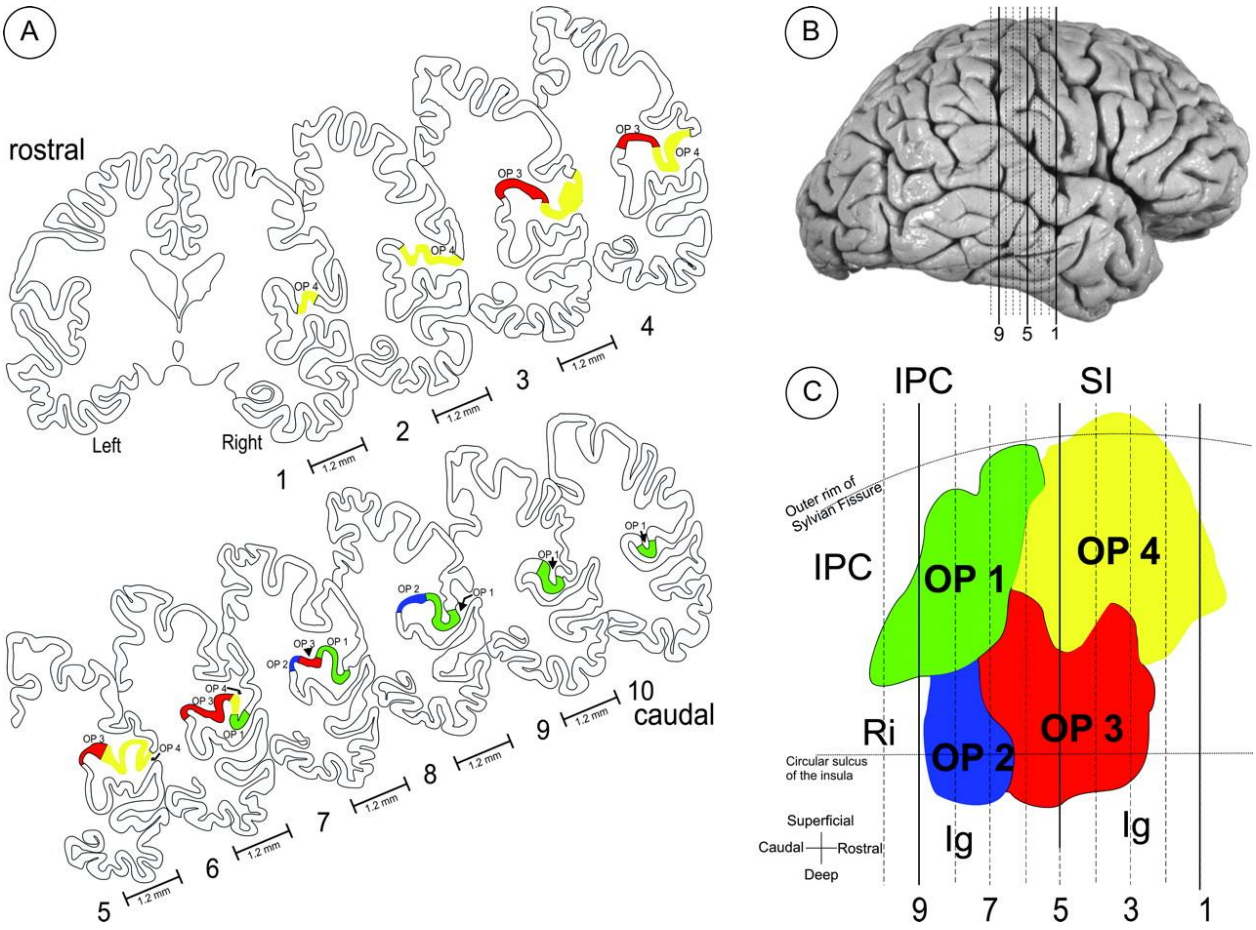


Figure 4. Location of OP2 in the right cerebral cortex. Areas in the parietal operculum are shown in serial coronal sections (A), with OP2 depicted in blue, from the right lateral hemisphere (B). The section numbers correspond to the numbers in the flat map (C). Simon Eickhoff, et al., The Human Parietal Operculum. I. Cytoarchitectonic Mapping of Subdivisions, Cerebral Cortex, 2006, Volume 16, Number 2, Page 262, by permission of Oxford University Press.

Positron emission tomography was used to identify the temporoparietal cortex, insula, putamen, and anterior cingulate cortex as regions activated in response to cold water irrigation of the peripheral vestibular system.(Bottini et al., 1994) A similar response was observed in

response to caloric testing.(Emri et al., 2003) Warm water irrigation activated the superior frontal gyrus and sulcus, precentral gyrus, inferior parietal lobule, and supramarginal gyrus, as well as the anterior insula and anterior cingulum.(Dieterich et al., 2003) Activations in these regions was mediated by the hand dominance of the subject and the side of caloric irrigation.(Dieterich et al., 2003) The greatest activation was seen when the side of hand dominance and caloric irrigation were ipsilateral. Somatosensory areas of the perisylvian cortex, insula, retroinsular cortex, temporoparietal junction, and somatosensory area II are activated by both caloric vestibular stimulation and mechanical neck vibration.(Bottini et al., 2001) Cortical activation in the middle and posterior insula and inferior parietal lobule was lateralized based on the direction of nystagmus.(Naito et al., 2003) Deactivation of the parieto-insular cortex and inferior parietal lobule was found during fixation (suppressing the nystagmus), further evidence of an inhibitory vestibular-visual interaction.(Naito et al., 2003)

Magnetoencephalography has been used to identify activation of the PIVC in response to optokinetic and caloric stimulation.(Hegemann, 2003) Electroencephalography recorded during anteroposterior sway about the ankle joints produced a burst of gamma activity in fronto-central electrode sites (Fz, F4, FCz, Cz, and C4) 200 milliseconds prior to reaching the anterior limit of stability and initiating posterior postural sway.(Slobounov, Hallett, Stanhope, & Shibasaki, 2005) This supports the theory that postural adjustments may be cortically controlled, and are not just reflexive muscle responses.(Slobounov et al., 2005)

Functional NIRS data revealed increased activation in the superior temporal gyrus and supramarginal gyrus at the temporoparietal junction during a video game skiing task.(Karim et al., 2012) This response was elongated for 20-30 seconds, which may represent adaptation of the vestibular cortex to the simple balance task.(Karim et al., 2012). Functional NIRS has also

shown increased cerebral activation in the prefrontal cortex (to include the dorsolateral prefrontal cortex and frontal eye field) in response to external perturbation, regardless whether it was preceded by an auditory signal.(Mihara et al., 2008) With an auditory warning signal, increased cerebral activation was seen in the right posterior parietal cortex and supplementary motor area.(Mihara et al., 2008) This activation may indicate a shift in visuospatial attention and preparation for foot/ankle movement, respectively, to maintain postural control.(Mihara et al., 2008) Increased cerebral activation in the supplementary motor area was also seen when balancing on a balance board,(Herold et al., 2017) highlighting the role of the cerebral cortex in postural control.

In summary, different neuroimaging modalities have been used to study cortical regions related to the integration and reweighting of visual, vestibular, and somatosensory afferent information for postural control. Imaging of the vestibular cortex (the region of the temporoparietal junction) has included fMRI, PET, MEG, EEG, and fNIRS. There is evidence of an inhibitory vestibular-visual interaction that lends support to sensory re-weighting. There is activation of the striate and extrastriate visual cortex, to include motion-sensitive areas MT/V5 and MST (intersection of Brodmann areas 19 and 37) in the temporo-occipital junction, with deactivation in the vestibular cortex in the areas of the posterior insula and retroinsular regions.(Brandt et al., 1998; Deutschländer et al., 2002; Deutschländer et al., 2004) It is not known if this same inhibitory vestibular-visual interaction occurs in patients with complaints of visual vertigo. Such changes in regions of cortical activation can be indirectly measured using fNIRS, which is based on changes in cortical blood flow.

2.5 CORTICAL BLOOD FLOW

Dynamic changes occur in blood flow, HbO_2 and Hb concentration, and metabolism during cortical activation. These changes are a shift from the resting physiological state of the brain. Functional NIRS can be used to image these regional changes in HbO_2 and Hb concentration during brain activity. An understanding of cortical blood flow is necessary for interpreting the hemodynamic response observed with this neuroimaging modality.

2.5.1 Cerebral physiology at rest

While the brain is never actually resting, this terminology is meant to imply the cerebral physiology preceding a stimulus or task that would result in cortical activation or deactivation. In its steady state, cerebral blood flow must deliver oxygen and glucose and remove carbon dioxide, lactic acid, and other byproducts of metabolism.(Kandel et al., 2000) Cerebral blood vessels autoregulate blood flow by two means.(Kandel et al., 2000) The first way is by changing their diameter; arterioles constrict or dilate in response to changes in blood pressure.(Kandel et al., 2000) This results in constant blood flow with the mean arterial pressure ranging from 60 to 150 mmHg.(Kandel et al., 2000) The second way cerebral blood vessels autoregulate is by blood and tissue gasses and pH. When carbon dioxide is increased, arterioles dilate and blood flow increases; the reverse is also true.(Kandel et al., 2000) The mechanism for vasodilation in response to carbon dioxide may be due to an increase in pH.(Kandel et al., 2000) When oxygen is increased, arterioles constrict and blood flow decreases, though this response is less prominent than the response to carbon dioxide.(Kandel et al., 2000) These mechanisms are important for maintaining homeostasis.

2.5.2 Cerebral physiology during activation

During cortical activation there is an increased energy demand with increased consumption of glucose and oxygen. Vasodilation results in increased blood flow, blood volume, and oxygenation of hemoglobin.(Kleinschmidt et al., 1996) The difference in the supply (oxygen delivery) and demand (oxygen consumption) during brain activation produces changes in the oxygenation of the blood. Together, the above changes are referred to as the hemodynamic response.

In the region of cerebral activation, increased blood flow results in decreased oxygen extraction as a result of increased blood velocity producing a decreased transit time of hemoglobin in the capillary.(Buxton, Wong, & Frank, 1998) Focal hyper-oxygenation occurs due to the increased blood flow, which exceeds the oxygen consumption (known as cerebral metabolic rate of oxygen [$CMRO_2$]).(Boden et al., 2007; Buxton et al., 1998) The increased blood flow is approximately three times larger than the increased $CMRO_2$; the increased blood volume is best reflected in the HbO_2 signal.(Boden et al., 2007) This is in agreement with Kleinschmidt et al., who stated that the concentration of HbO_2 is much higher than that of Hb and is more reflective of changes in blood flow and volume than oxygenation.(Kleinschmidt et al., 1996) Following the increased blood flow is an increase in regional venous outflow that ultimately matches the inflow. The venous outflow removes the Hb more rapidly than it is produced during oxidative metabolism, which produces a temporal delay in the Hb signal that mirrors that of the venous outflow.(Boden et al., 2007) Just as an increase in cortical blood flow is assumed to signify cortical activation, a decrease in cortical blood flow is assumed to signify deactivation.(Shulman et al., 1997)

Changes in HbO_2 precede changes in Hb for the sensorimotor system by an average of 1.6 seconds.(Boden et al., 2007) This relationship is not present in the visual system.(Boden et al., 2007) The differences seen in the cortical regions may be due to the active (motor task) versus passive (viewing task) nature of the stimuli.(Boden et al., 2007) The magnitude of latency can be reduced when NIRS signals are corrected for systemic hemodynamic confounds, but it remains present.(Boden et al., 2007)

In summary, during cortical activation there are dynamic changes in blood flow, HbO_2 and Hb concentration, and metabolism above the resting physiological state of the brain. Functional NIRS can be used to detect these regional changes in HbO_2 and Hb concentration during brain activity. Changes in HbO_2 and Hb concentration in the bilateral temporal lobes during optic flow has not been explored using fNIRS, especially not during quiet stance. Differences in changes in HbO_2 and Hb concentration in the bilateral fronto-temporo-parietal lobes and occipital lobes between healthy individuals and those with complaints of visual vertigo has not been investigated or correlated with changes in postural sway.

3.0 USE OF NEAR-INFRARED SPECTROSCOPY TO EXAMINE THE EFFECT OF YAW OPTIC FLOW ON CEREBRAL ACTIVATION AND THE PERCEPTION OF VECTION

Vection is essential for spatial orientation, locomotion, and navigation. To date, no studies have used fNIRS to explore optic flow that induces the perception of vection, which is important for the judgement, control and guidance of self-motion.(Palmisano et al., 2015) Wijeakumar et al. explored cortical activation in the primary visual cortex in response to a moving visual stimulus.(Wijeakumar et al., 2013) Their study did not investigate the perception of vection and was not designed to assess cortical activation in the middle temporal region, the area of the brain that responds preferentially to optic flow in humans.(Lappe, 2009) fNIRS may provide a means to explore the mechanisms of cortical processing of optic flow information designed to induce vection, and whether or not the resulting cortical activation is mediated by the presence of a fixation cross.

A better understanding of the normal mechanisms of cortical processing of optic flow information is a necessary first step in establishing optimal rehabilitation regimens that include visually-based habituation exercises. There is no evidence to support or refute the use of a fixation cross during habituation to optic flow. Whether or not a patient is asked to fixate on a target during progressive exposure to optic flow is at the discretion of the treating physical therapist, which leads to variation in practice patterns and patient outcomes. Evidence for the

use of a fixation cross during treatment using optic flow would help to standardize delivery of optic flow as a physical therapy intervention.

3.1 SPECIFIC AIMS AND HYPOTHESES

3.1.1 First specific aim

To examine the effect of pseudo-random and constant velocity optic flow on cerebral activation, vection perception, and postural sway in healthy adults. The hypotheses related to this specific aim were:

H1.1 Cerebral activation in the bilateral temporal and occipital lobes, as measured by fNIRS, will be greater during constant velocity than pseudo-random optic flow.

H1.2 Vection perception (ratings of intensity), as measured by item 14 of the MSAQ, will be greater during constant velocity than pseudo-random optic flow.

H1.3 Postural sway, as measured by the RMS and NPL of COP movements, will be greater during constant velocity than pseudo-random optic flow.

3.1.2 Second specific aim

To examine the effect of fixation on cerebral activation, perception of vection, and postural sway during pseudo-random and constant velocity optic flow in healthy adults. The hypotheses related to this specific aim were:

H2.1 Cerebral activation in the bilateral temporal and occipital lobes, as measured by fNIRS, will be greater with fixation than without fixation.

H2.2 Vection perception (ratings of intensity), as measured by item 14 of the MSAQ, will be greater with fixation than without fixation.

H2.3 Postural sway, as measured by the RMS and NPL of COP movements, will be greater with fixation than without fixation.

3.2 METHODS

This experiment was performed in order to accomplish the specific aims described above. Healthy subjects (7 males and 8 females, mean age 41 years old) were exposed to optic flow while cerebral activation and postural sway data were recorded (Figure 5). All data were collected in the Medical Virtual Reality Center.

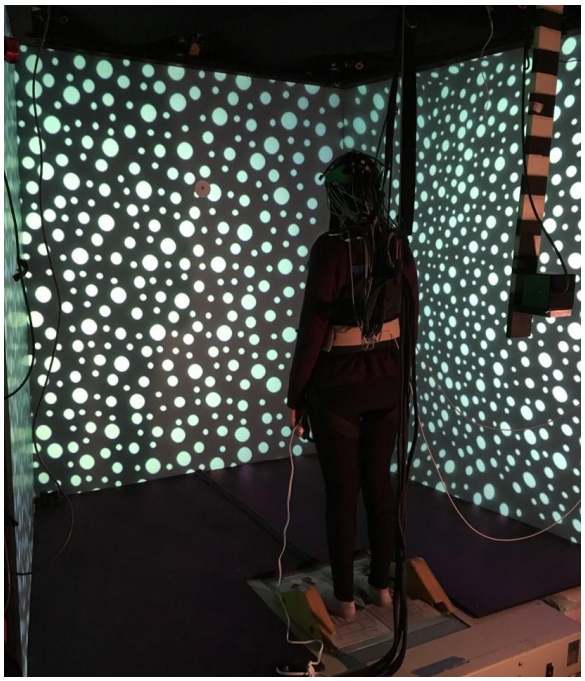


Figure 5. Experimental setup for study one. The subject stood on a force plate and was exposed to optic flow in a three-screen wide field of view virtual environment. Subjects wore an electromagnetic tracker on top of their head and on their back, and a NIRS head cap.

3.2.1 Study design

This study consisted of an ABABA design, where A was comprised of stationary dots and B was comprised of optic flow in the yaw plane. This design provided two opportunities (B_1 and B_2 phases) to evaluate the effects of optic flow. Four trials were conducted at each of two experimental visits (Figure 6).

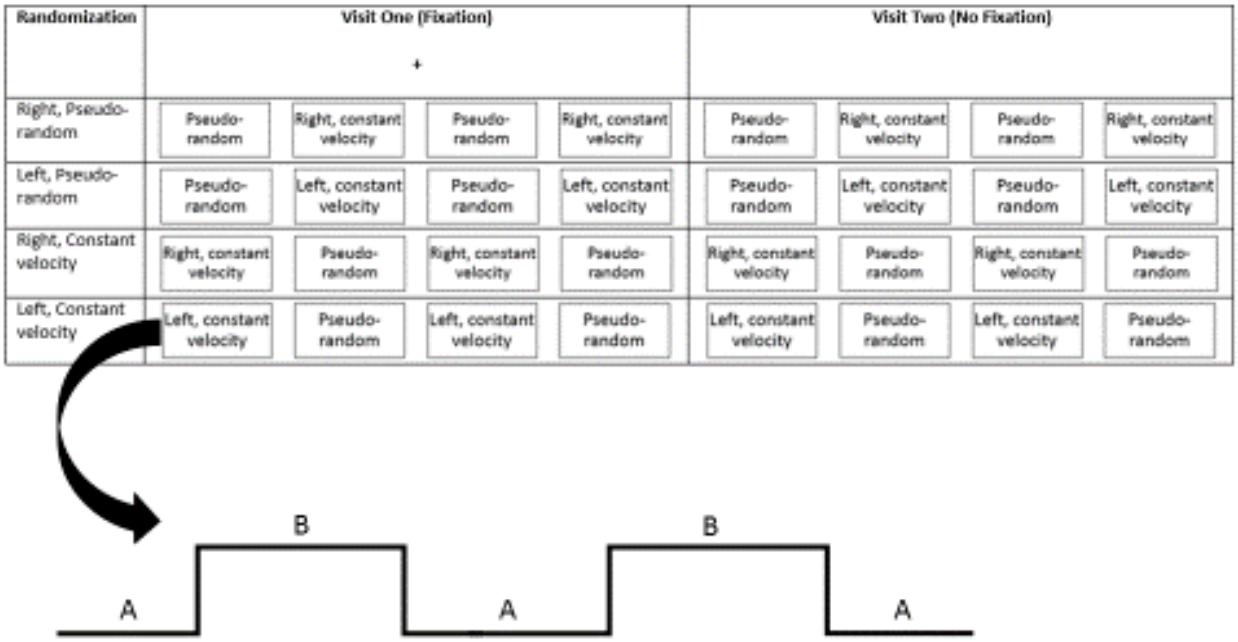


Figure 6. Experimental design for study one. The subject was randomized to one of four groups. A fixation cross was viewed during Visit One, but not during Visit Two. For each of the four trials (depicted in the rectangles), an ABABA design was used for viewing the visual stimulus. The visual stimulus had three stationary dot phases (A) and two optic flow phases (B). For example, a subject randomized to the "Left, Constant velocity" group would complete four trials (leftward optic flow, pseudo-random optic flow, leftward optic flow, and pseudo-random optic flow) with a fixation cross during Visit One.

3.2.2 Inclusion criteria

Healthy men and women between the ages of 18 and 85 were eligible to participate. Subjects were recruited from the University of Pittsburgh and surrounding area. Subjects were asked to abstain from alcohol for 48 hours before the experimental visits. Alcohol is known to enhance vection (Seno & Nakamura, 2013) and increase postural sway (Nieschalk et al., 1999), and thus would be a confounding factor in our study. In addition, subjects were asked to get a good night's sleep (7-8 hours) the night before testing. Items 7 ("I felt drowsy") and 10 ("I felt

tired/fatigued") of the MSAQ were used to capture sopite-related motion sickness symptoms(Gianaros et al., 2001). Fatigue related to lack of sleep would, therefore, be a confounding factor in our study. Additionally, sleep deprivation is known to negatively affect the postural stability of adults (Aguiar & Barela, 2014).

3.2.3 Exclusion criteria

Subjects were ineligible to participate in the study if they had: a history of otologic or neurologic disease; history of migraine; corrected binocular vision worse than 20/40, macular degeneration, or glaucoma; results of screening tests that indicated vestibular asymmetry or loss; history of excessive motion sickness; medication use that may affect balance (e.g., antipsychotics, barbiturates, benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants); unwillingness to abstain from alcohol for 48 hours prior to testing; known pregnancy; and/or body weight greater than 118 kilograms. A history of migraine was determined based on a previous diagnosis or as a result of a questionnaire asked during the phone screening interview (Appendix A). Excessive motion sickness was determined using the Motion Sickness Susceptibility Questionnaire (MSSQ) revised (Appendix B). A score greater than 135.8 for women or 97.7 for men was set as the cutoff for excessive motion sickness, as these are the established mean MSSQ scores plus two standard deviations.(Golding, 1998)

The MSSQ revised refined the original instrument created by Reason and Brand, and can predict motion sensitivity in provocative environments.(Golding, 1998) The questionnaire has two sections: experiences during childhood (under 12 years of age) and experiences during the last decade.(Golding, 1998) The subject rates how frequently they have experienced different modes of transportation, how frequently they felt sick or nauseated, and how frequently they

vomited. The MSSQ raw score is equivalent to the addition of the scores on the two sections.(Golding, 1998) The section scores are equivalent to: (2.64 × (total sickness score child or adult) × 9)/(number of types of transport or entertainment experienced as a child or adult).(Golding, 1998) There has been some use of the MSSQ in the published (approximately 10 peer-reviewed journal articles) and unpublished (approximately 1 doctoral dissertation) literature. The psychometric properties of the MSSQ have been thoroughly reported.(Golding, 1998) Internal reliability of the MSSQ was 0.86, and the correlation between the child and adult sections was $r = 0.65$ ($p < 0.001$).(Golding, 1998) Predictive validity of the MSSQ for motion sickness tolerance was $r = 0.45$.(Golding, 1998) The test-retest reliability was not assessed. Normative data has been published on the MSSQ based on findings from university students.(Golding, 1998)

3.2.4 Optic flow stimulus

The visual stimulus consisted of 720 white dots on a black background. The dots were of three sizes (3.4, 2.5, and 1.5 degrees of visual angle) and covered approximately 20 percent of the total area to remain consistent with studies conducted by Brandt et al. and Deutschländer et al. The visual stimulus used in these two studies induced vection in all subjects.(Brandt et al., 1998; Deutschländer et al., 2004) For optic flow in the yaw plane, there were two motion stimuli: one stimulus was pseudo-random left and right movement (sum of four sines: frequency = $\pi/31$, $\pi/11$, $\pi/7$, $\pi/5$ Hz) at an RMS velocity of 40 degrees per second; and the other stimulus was unidirectional movement at a constant velocity of 40 degrees per second. The sum of four sines was used to produce changes in the velocity that would be difficult to anticipate.(Andersen & Dyre, 1989) The baseline (control) condition was stationary dots. The visual stimulus was back-

projected onto a three-screen wide field of view (180 degrees horizontal and 70 degrees vertical). Subjects faced the front screen that was 1.5 meters away. As part of the ABABA design, each block was presented for 1 minute for a total of 5 minutes for each trial.

3.2.5 Study protocol

This study was approved by the University of Pittsburgh Institutional Review Board (PRO14080255). Subjects provided informed consent at the start of the Screening Visit, before undergoing formal screening to determine if the inclusion and exclusion criteria were met. The screening for exclusion criteria consisted of demographic information, hand dominance, completion of the MSSQ revised, visual acuity testing, neurologic examination, subjective visual vertical testing (bucket test (Zwergal et al., 2009)), checking for cerumen, and tests for vestibular hypofunction. The tests for vestibular hypofunction were caloric testing, electronystagmography, and rotation testing. Vestibular evoked myogenic potentials testing was not performed. It was decided that normal otolith function would be assumed if the subject reported no history or otologic or neurologic disease, caloric testing was normal, and if performance on the bucket test (10 trials) was normal.

The bucket test is a simple bedside test for assessment of subjective visual vertical and has excellent inter-test (0.89-0.90) and intra-test (0.92) reliability.(Zwergal et al., 2009) Its clinical utility as a screening test, however, has been called into question.(Cohen & Sangi-Haghpeykar, 2012) While good cut-points on receiver operating characteristics analyses for differentiating normal subjects from those with unilateral hypofunction or benign paroxysmal positional vertigo could not be established with the bucket test, it was able to quantify the deviation in subjective visual vertical.(Cohen & Sangi-Haghpeykar, 2012) Thus, we used the

bucket test as one part of the formal screening, and evaluated its results amongst all of the examination findings for determination of a subject's eligibility for inclusion in the study.

Visit One was the first of two experimental visits. Four trials were conducted, with the subject viewing a fixation cross during all trials. The fixation cross was located at eye level. The direction of motion of the dots (right versus left) and the order of the type of motion (pseudo-random versus constant velocity) was randomized using the Research Randomizer (https://www.randomizer.org/) internet program. Allocation concealment was preserved by keeping the random assignments in paper envelopes until the start of Visit One. Subjects stood in stocking feet, with feet shoulder-width apart. A safety harness that was tethered to the ceiling was worn. The tether was not so tight that it would hinder postural sway or provide additional sensory feedback to the subject. The subject held the throttle for rating intensity of vection in their left hand. During all of the trials the subject was instructed to: "Look straight ahead at the fixation cross. Push the throttle up, if and when you feel like you are moving. When you don't feel like you are moving, or moving very little, keep the throttle near the bottom. When you feel like you are moving the most, keep the throttle near the top. You can move it anywhere in between depending on how much you feel like you are moving. Push the throttle down if it decreases or stops." Subjects were given a 5 minute seated rest break between trials.

Visit Two was the second of two experimental visits. Four trials were conducted, with the subject looking straight ahead during all trials. The direction of motion of the dots and the order of the type of motion was conducted in the same direction and order used during the previous visit. During all of the trials the subject was instructed to: "Look straight ahead in a relaxed manner at the dot pattern." They pushed the throttle up and down as they did during the

previous visit. Subject positioning also remained the same and subjects were again given a 5 minute seated rest break between trials.

3.2.6 Outcome measures

Cerebral activation was measured using the NIRS head cap. Perception of vection was quantified as part of the MSAQ. The intensity and duration of perception of vection was captured using a throttle device. Postural sway was measured using a force plate. Each of these outcome measures is described in greater detail below.

3.2.6.1 Near-infrared spectroscopy

A 32-channel continuous wave NIRS instrument (CW6 Real-time system; TechEn, Inc.; Milford, MA) was used to record changes in HbO_2 and Hb at 830 nm and 690 nm, respectively.(Cope et al., 1988; Strangman et al., 2003) The technique is based on the modified Beer-Lambert law(Cope et al., 1988), which has the equation:

$$I = I_0 e^{-\mu_a(\lambda) DPFx + G}$$

where I is the detected light, I_0 is the incident light, μ_a is the absorption coefficient, and $DPFx$ is the differential path length factor, and G is a geometry-dependent factor accounting for the fact that only some of the light scattered in the tissue is detected. The variable being estimated is the absorption coefficient. The NIRS head cap consisted of 11 sources and 20 detectors located over the bilateral fronto-temporo-parietal lobes and occipital lobes (Figure 7). Strong cardiac oscillations observed in the raw signals indicated good coupling between the probe and the scalp. Data from 72 source-detector combinations (36 source-detector combinations at two

wavelengths) was collected at a sampling rate of 20 Hz using nearest-neighbor geometry with 2.8 centimeter spacing between sources and detectors. Custom data acquisition software that allowed for real-time visualization of brain activity was used.(Abdelnour & Huppert, 2009) Stimulus events (the changes between the ABABA phases of the trial) were manually recorded by the research technologist using a feature of the acquisition software.

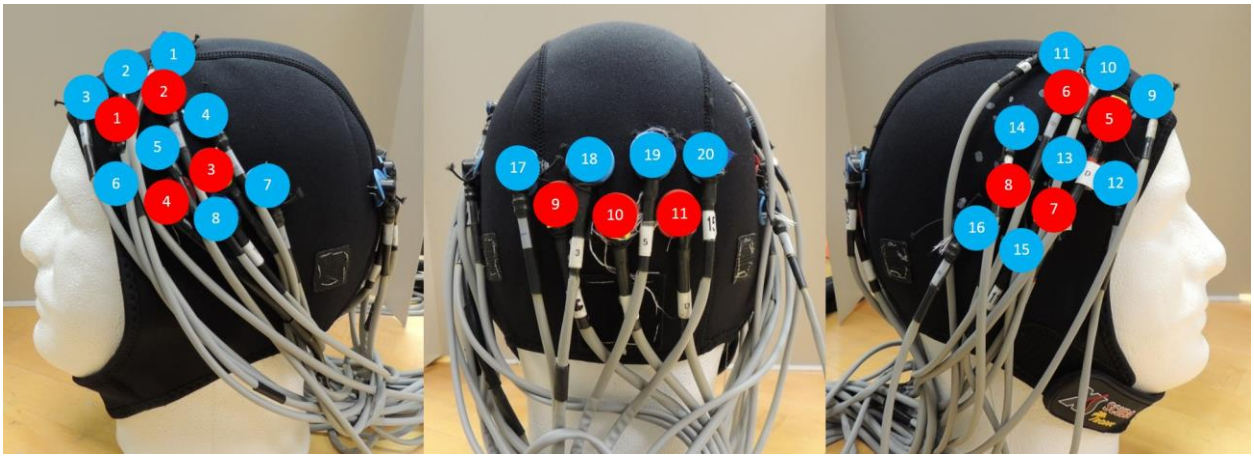


Figure 7. Near-infrared spectroscopy cap. The subject wore a NIRS head cap that consisted of 11 sources (red) and 20 detectors (blue) on the scalp, distributed between the left fronto-temporo-parietal (left), occipital (center), and right fronto-temporo-parietal (right) regions.

3.2.6.2 Motion Sickness Assessment Questionnaire

The MSAQ (Appendix C) was administered at baseline, following each of the four trials, and at the conclusion of the experimental visits. The investigator read each of the sixteen statements from the MSAQ, and asked the subject to rate the intensity of the items describing their experience on a scale ranging from one to nine. If the subject responded with a two or higher, the investigator further probed by asking the subject during what period of the trial the item was experienced. This latter question was not part of the MSAQ as originally described, however, it allowed for a temporal investigation of the subject's report of symptoms. Pilot testing revealed that handouts (Appendix C) helped clarify the rating scale for the MSAQ items. A handout with

a graphic depicting the ABABA phases of the trial helped subjects identify when they perceived symptoms during the course of the trial.

3.2.6.3 Throttle for vection intensity and duration

Palmisano et al. cautioned that simultaneous measurement of vection and postural sway verbally or using a throttle or joystick might introduce a motion artifact.(Palmisano et al., 2014) Therefore, our throttle was designed to be small, lightweight, and easy to operate. It measured 7.62 x 3.81 x 2.22 centimeters and weighed less than 0.1 kilograms. Our throttle is unique in that it allowed for the simultaneous quantification of vection intensity and duration. Voltage was recorded based on the position of the throttle; before beginning the experiment, the range of possible values was set by moving the throttle between the bottom and top limits to establish the measurement scale. Subjects slid a throttle up when they perceived vection and kept the throttle up for the duration self-motion was experienced. The throttle was held in the left hand to remain consistent with previous studies.(Tanahashi et al., 2007)

3.2.6.4 Postural sway

Subjects stood on a modified NeuroTest platform (NeuroCom International, Inc., Clackamas, OR) that measured ground reaction forces at a sampling rate of 100 Hz. The ground reaction forces were used to compute the COP. An electromagnetic tracking system (Polhemus Fastrak, Colchester, VT) was used to record postural sway. Subjects wore receivers on top of their head (Figure 8) and on a back belt placed at the level of the iliac crests. The space was defined with the x-axis anteriorly, y-axis rightward, and z-axis geotropic. The position of the receivers was measured at a sampling rate of 60 Hz. This postural sway data was used to compute the RMS and NPL of head, hips, and center of pressure movements.

Figure 8. Subjects wore an electromagnetic tracker on top of their head (gray cube), over a NIRS head cap.

The RMS is the standard deviation of the displacement of the COP from the mean. It is calculated according to the following equation:

$$RMS = \sqrt{\frac{\sum_{j=1}^{N-1}(p_j - p_{avg})^2}{N}}$$

where: N is the total number of time samples, p_{avg} is the average across the time series, and p_j is the COP data at time j.

The NPL is a measure of the travel of the COP, well described by Donker et al. and Roerdink et al.(Donker, Ledebt, Roerdink, Savelsbergh, & Beek, 2008; Roerdink, Beek, Greven, & Donker, 2007) It describes the average velocity of the postural sway. The NPL is the total path length divided by the time, and is calculated according to the following equation:

$$NPL = \frac{\sum_{j=1}^{N-1}|p_{j+1} - p_j|}{t}$$

where: t is the time duration, N is the total number of time samples, and p_j is the COP data at time j.

3.2.7 Statistical analyses

Data were analyzed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY) and MATLAB (Mathworks, Natick, MA).

3.2.7.1 Near-infrared spectroscopy

NIRS data was analyzed based on a general linear model with a boxcar function of the timing and duration of the optic flow as a regressor. First, MATLAB was used to pre-process the data. This involved marking the onset of the optic flow phases during the trials. Following pre-processing, the optical data was down sampled from 20 Hz to 4 Hz using a custom-built MATLAB-based acquisition software program.(Barker, Aarabi, & Huppert, 2013) Optical data recorded as changes in light intensity as a function of time was converted to optical density. The modified Beer-Lambert law was applied to convert the data from optical density to concentration change.(Cope et al., 1988) A partial path length correction of 0.1 (differential path length factor = 6 and partial volume factor = 60) was used.(Strangman et al., 2003) The time-course of hemoglobin changes for each source-detector pair was analyzed using a general linear model, where β is the coefficient (weight) of the optic flow stimulus condition for the source-detector channel.

To reduce effects of motion artifacts and systemic physiology, an iteratively auto-regressively whitened, weighted least squares model was used.(Barker et al., 2013) This regression model uses an n^{th} order auto-regressive filter determined by an Akaike model-order

selection to whiten both sides of the general linear model equation. Basically, an iterative procedure is used to whiten serially correlated noise and reweight statistical outliers using a robust regression procedure using a bi-square weighting function. This reweighting reduces the impact of motion-artifacts since these points are generally statistical outliers from a normal distribution following auto-regressive whitening. Using this model, the regression coefficients and their error-covariance ($Cov\beta$) are estimated, which is used to define statistical tests between optic flow stimulus conditions. The subject-level statistical analysis investigated if the optic flow stimulus elicited a significant brain activation compared with the stationary visual stimulus. The regression model was solved sequentially for each data file for each of the 15 subjects. All source-detector pairs within a file were solved concurrently, yielding a full covariance model of the noise, which was used in the group-level analysis. T-tests were conducted to determine if the regression coefficients were statistically non-zero.

Group-level statistical analysis was performed using a linear mixed-effects model, using the task-related regression coefficients from the subject-level general linear model as the dependent variable and subject included as a random effect. A modified version of the MATLAB function fitLME (linear mixed effects model estimator) was used to solve the weighted maximum likelihood estimate of the parameters. The model was whitened using the error-covariance from the subject-level general linear model. A false discovery rate correction(Benjamini & Hochberg, 1995) was applied to control for Type I error, with the significance level set at 0.05 ($q \leq 0.05$). The group-level statistical analysis investigated the effect of fixation versus no fixation during constant velocity optic flow using a linear mixed-effects model with optic flow condition as the fixed effect and subjects as a random effect.

The spatial arrangement of detectors on the scalp was used to approximate the location of cerebral activity.(Boas et al., 2004) The location of the sources and detectors was registered to an anatomical MRI head Colin27 atlas(Holmes et al., 1998) using an affine registration algorithm.(Abdelnour & Huppert, 2009) This registration and a finite-element model of light diffusion was used to build a forward model to describe the sensitivity of the head cap to underlying brain regions.(A. Abdelnour & Huppert, 2009) Three regions of interest were explored (right fronto-temporo-parietal lobe, left fronto-temporo-parietal lobe, and occipital lobes). Then, image reconstruction was performed based on a model that used wavelets to model the surface of the cerebral cortex.(Abdelnour, Schmidt, & Huppert, 2009) A group-level image was reconstructed that best modeled all of the subjects' data.

3.2.7.2 Motion Sickness Assessment Questionnaire

The total symptom score was calculated as the percentage of total points scored (sum of points from all items/144) × 100.(Gianaros et al., 2001) The subscale scores were calculated as the percent of points scored within each category, such as (sum of gastrointestinal items/36) × 100; (sum of central items/45) × 100; (sum of peripheral items/27) × 100; and (sum of sopite-related items/36) × 100.(Gianaros et al., 2001) The average total symptom scores and subscale scores during pseudo-random and constant velocity optic flow were compared using dependent t-tests. The significance level was set at $\alpha = 0.05$. The dependent t-tests were one-tailed due to the directionality of the hypotheses.

3.2.7.3 Throttle for vection intensity and duration

Similar to the methods of previous studies,(Seno & Nakamura, 2013; Seno & Sato, 2009) onset latency and accumulated vection duration were calculated. Onset latency and duration were

defined as described by Seno et al.(Seno et al., 2010) Dependent t-tests were used to analyze the onset latency and accumulated vection duration between pseudo-random and constant velocity optic flow. The significance level was set at $\alpha = 0.05$. The dependent t-tests were one-tailed due to the directionality of the hypotheses.

3.2.7.4 Postural sway (secondary data analysis)

Anterior-posterior and medial-lateral translation data from the electromagnetic trackers on the head and hips were digitally low-pass filtered using zero-phase implementation of a fourth order Butterworth filter with a cutoff frequency of 2 Hz. Filtered data was then used to calculate the RMS and NPL of the anterior-posterior and medial-lateral movement of the head and hips.

Data from the force plate was post-processed using MATLAB to obtain COP measures. The COP was digitally low-pass filtered and zero-meaned. Low-pass filtering was achieved through zero-phase implementation of a fourth order Butterworth filter with a cutoff frequency of 2 Hz. Filtered data was then used to calculate the RMS and NPL of the anterior-posterior and medial-lateral movement of the COP.

This data was checked for normality using the Shapiro-Wilk test in addition to examination of the histograms, q-q plots, box plots, skewness, and kurtosis. If the *p*-value for the Shapiro-Wilk test was greater than .05, the data were normally distributed. Linear Mixed-Effects Models, which are robust to violations of normality, were used to test how the main effect of fixation contributed to observations of postural sway.

Differences between conditions (fixation versus no fixation), types of motion (pseudo-random versus constant velocity) and visual stimuli periods (optic flow versus stationary surround) were examined using linear mixed-effects models. In total, twelve models were estimated: anterior-posterior head NPL, anterior-posterior head RMS, medial-lateral head NPL,

medial-lateral head RMS, anterior-posterior hips NPL, anterior-posterior hips RMS, medial-lateral hips NPL, medial-lateral hips RMS, anterior-posterior COP NPL, anterior-posterior COP RMS, medial-lateral COP NPL, and medial-lateral COP RMS. Akaike's Information Criterion (AIC) and Schwartz's Bayesian Information Criterion (BIC) were used to select a model with the most appropriate covariance structure. Unstructured, compound symmetry, compound symmetry heterogeneous, first-order autoregressive heterogeneous, and Toeplitz heterogeneous were all explored. Using a compound symmetry heterogeneous covariance structure, the models converged and had acceptable AIC and BIC values. A restricted maximum likelihood approach was used.

As the findings were consistent for the types of motion (first and second trial of the same visual stimuli, e.g. pseudo-random optic flow observed during second and fourth trials) and visual stimuli periods (three stationary and two optic flow), the mean values for the dependent variables were combined for type of motion and period to reduce the number of variables. The three stationary visual stimuli periods were pooled into one stationary visual stimuli variable. The two optic flow visual stimuli periods were pooled into one optic flow visual stimuli variable. Repetitions of trials for the same type of visual motion were pooled together, reducing four conditions into two conditions. The fixed effects were condition (fixation versus no fixation), type of motion (pseudo-random versus constant velocity), and period (optic flow versus stationary visual field), and the interaction effects were condition by type of motion, condition by period, and type of motion by period. Subject was included as a random effect. Post-hoc testing consisted of pairwise comparisons based on the estimated marginal means. The significance level was set at $\alpha = 0.05$.

3.3 RESULTS

Twenty-three healthy subjects were recruited and screened for inclusion in the study. Fifteen subjects (7 males and 8 females; mean age 41 years old, range 20-67; 13 right-handed, 1 left-handed, and 1 ambidextrous) completed both experimental visits. One individual who was eligible to participate withdrew prior to the experimental visits due to a change in health status, and seven individuals were disqualified from participating based on the exclusion criteria.

3.3.1.1 Near-infrared spectroscopy

Statistical analyses using a general linear model revealed significant activation in the three regions of interest when viewing optic flow with a fixation target compared to a stationary visual field (Table 2). A similar trend was seen without fixation, however, decreased Hb signals in the left fronto-temporo-parietal lobe (T = -0.96, p = 0.369, FDR-corrected) and decreased HbO2 signals in the right fronto-temporo-parietal lobe (T = -1.85, p = 0.080, FDR-corrected) were not statistically significant.

Table 2. Change in cerebral activation when viewing optic flow compared to a stationary visual field. Beta = regression coefficients; DF = degrees of freedom; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Visit	Region of Interest	Chromo-phore	Beta	Standard Error	DF	T	*p*	*q*
Fixation	Left fronto-temporo-parietal	HbO_2	1.447	0.154	1796	9.41	< 0.0001	< 0.0001*
		Hb	-0.618	0.089	1796	-6.97	< 0.0001	< 0.0001*
	Right fronto-temporo-parietal	HbO_2	0.800	0.144	1796	5.55	< 0.0001	< 0.0001*
		Hb	-0.756	0.082	1796	-9.24	< 0.0001	< 0.0001*
	Occipital	HbO_2	0.848	0.333	716	2.55	0.0110	0.0176*
		Hb	-1.063	0.160	716	-6.62	< 0.0001	< 0.0001*
No Fixation	Left fronto-temporo-parietal	HbO_2	0.575	0.157	1796	3.65	0.0003	0.0006*
		Hb	-0.093	0.097	1796	-0.96	0.3380	0.3687
	Right fronto-temporo-parietal	HbO_2	-0.309	0.167	1796	-1.85	0.0642	0.0800
		Hb	-0.211	0.097	1796	-2.18	0.0294	0.0440*
	Occipital	HbO_2	1.383	0.301	716	4.59	< 0.0001	< 0.0001*
		Hb	0.370	0.141	716	2.62	0.0089	0.0152*

Statistical analyses using a linear mixed-effects model to explore fixation versus no fixation revealed significant activation in the bilateral fronto-temporo-parietal lobes (Table 3). Increased HbO2 and decreased Hb signals were noted in the left fronto-temporo-parietal lobe. A similar trend was seen in the right fronto-temporo-parietal lobe, however, the decreased Hb signals were not statistically significant (T = -0.92, p = 0.426, FDR-corrected). Decreased Hb signals were also noted in the occipital lobe with fixation compared to without fixation, though changes in HbO2 were not significant (T = -0.36, *p* = 0.725, FDR-corrected). Estimated spatial

maps (t-test) of the oxyhemoglobin data for the change in cerebral activation between fixation and no fixation conditions using all source-detector combinations for the three regions of interest are shown in Figure 9.

Table 3. Change in cerebral activation when viewing optic flow moving unidirectionally in the yaw plane with a fixation cross compared to without a fixation cross. Degrees of freedom = 8,352. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Region of Interest	Chromophore	Beta	Standard Error	T	*p*	*q*
Left fronto-temporo-parietal	HbO_2	7.465	2.377	3.14	0.0016	0.0051*
	Hb	-8.769	2.026	-4.33	< 0.0001	< 0.0001*
Right fronto-temporo-parietal	HbO_2	8.414	2.970	2.83	0.0046	0.0092*
	Hb	-2.216	2.396	-0.92	0.3550	0.4260
Occipital	HbO_2	-0.468	1.329	-0.35	0.7247	0.7247
	Hb	-2.957	1.087	-2.72	0.0065	0.0098*

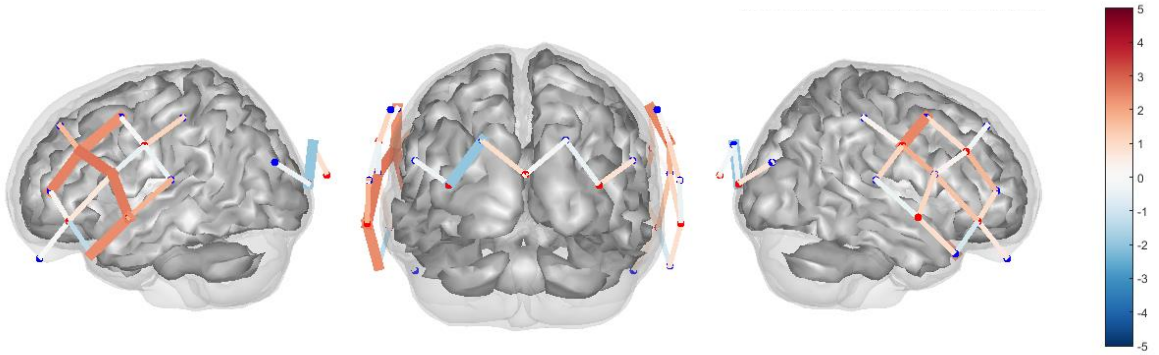


Figure 9. Estimated spatial maps (T-test) of the oxyhemoglobin data collected using fNIRS for the change in cerebral activation between fixation and no fixation conditions using all source-detector combinations. The color bar represents the results of the T-statistic (T-score). Areas in red indicate greater cerebral activation (increased

oxyhemoglobin) and areas in blue indicate lesser cerebral activation (decreased oxyhemoglobin) during the comparison. Thick lines indicate areas with significant activation ($p < 0.05$).

3.3.1.2 Motion Sickness Assessment Questionnaire

The MSAQ ratings were checked for normality using a Shapiro-Wilk test, and were found to be non-normally distributed. A Wilcoxon signed rank test indicated that ratings of vection intensity were not different between fixation (M = 2.55, SD = 2.00) and no fixation conditions (M = 2.50, SD = 1.66), Z = -.182, p = .855.

3.3.1.3 Throttle for vection intensity and duration

Data from the throttle was not able to be analyzed. The subject was not informed to reset the throttle (push it all the way down) between the ABABA phases. This resulted in an inability to compare the changes in vection intensity between subjects, as each subject may have had the throttle at a different baseline for the phases and trials tested. Therefore, the relationship between MSAQ and throttle device ratings of vection intensity during pseudo-random and constant velocity optic flow in healthy adults could not be explored.

3.3.1.4 Postural sway

Data from the electromagnetic tracker is still being analyzed. Data from the force plate was not able to be collected due to failure of three out of four load cells during the course of the experiment. Therefore, analysis of the NPL and RMS of center of pressure movement during pseudo-random and constant velocity optic flow in healthy adults with and without the presence of a fixation cross could not be explored.

3.4 DISCUSSION

This research was performed to better understand the processing of optic flow information when viewing optic flow in comparison to a stationary visual field, with and without the presence of a fixation cross. Study of this relationship was conducted by examining changes in cerebral activation using fNIRS, which revealed greater activation when viewing optic flow in comparison to a stationary visual field in the bilateral fronto-temporal-parietal and occipital lobes. Additionally, greater activation was seen in the bilateral fronto-temporo-parietal lobes when optic flow moving unidirectionally in the yaw plane was viewed with a fixation cross than without.

The mechanisms of cortical processing of optic flow information was previously limited to neuroimaging techniques that required the patient to lie supine and motionless during image acquisition. Functional MRI during yaw or pitch optokinetic stimulation revealed that the presence of a fixation target suppressed optokinetic nystagmus and resulted in increased activation in the supplementary eye field and anterior cingulate gyrus, unchanged activation in the visual cortex, decreased activation in most of the ocular motor areas, and suppressed activation in the anterior and posterior insula and the thalamus.(Dieterich et al., 1998) The anterior and posterior insula are deep within the lateral sulcus (underneath the fronto-temporo-parietal regions of interest in this study), and cannot be imaged with fNIRS. During unidirectional optic flow in the yaw plane viewed with a fixation cross, there was increased activation (increased HbO_2) in the bilateral fronto-temporo-parietal lobes in the region of the supramarginal gyrus. This region is involved in sensory reweighting of visual, vestibular, and proprioceptive system information.(Karim et al., 2013) Similar to this response to optic flow during quiet stance, fNIRS revealed increased activation in the superior temporal gyrus and

supramarginal gyrus at the temporoparietal junction during a video game skiing task.(Karim et al., 2012) There was no difference in HbO_2 changes in the occipital lobe, which may be explained by the presence of optic flow in both viewing conditions. The larger decrease in Hb signals in the occipital lobe during the no fixation condition is unclear at this time.

To date, no other studies have used fNIRS to explore optic flow and the perception of vection. Fixation is known to enhance the perception of vection. This may be explained by suppression of optokinetic nystagmus, which causes the visual stimuli to repeatedly move across the retina.(Tarita-Nistor et al., 2006) This may lead to greater afferent input for central processing in cortical regions responsive to visual motion and optic flow information. Visual stimuli appear to move faster when gaze is fixated on the static (black) background, than when smooth pursuit is used to follow the dots; this is referred to as the Aubert-Fleischl paradox.(Tarita-Nistor et al., 2006) Subjects perceived greater estimates of vection with higher velocity visual motion.(Boff et al., 1986) Our findings indicate that the presence of a fixation cross during coherently moving optic flow designed to induce vection increased cortical activation. Fixation may have suppressed the optokinetic nystagmus in our participants, leading to greater cortical processing of visual motion as indicated by increased oxyhemoglobin changes in comparison to viewing optic flow without fixation. Previous research found that the presence of a fixation cross during linear left to right optic flow decreased vection latencies and increased vection duration.(Tarita-Nistor et al., 2006) Decreased vection latencies were also found with fixation compared to without fixation during yaw and pitch optic flow.(Fushiki et al., 2000) However, there are some discrepancies in the literature regarding the influence of fixation on perception of vection; Stern et al. reported that fixation decreased ratings of vection.(Stern et al., 1990)

The MSAQ was originally developed to assess motion sickness as a multidimensional construct,(Gianaros et al., 2001) but was used in this study to quantify vection. In this sample of 15 healthy adults, no difference was found in subjective ratings of vection intensity using the MSAQ when the optic flow stimulus was viewed with and without the presence of a fixation cross. This suggests that item 14 of the MSAQ may not be sensitive to changes in perception of vection intensity. Although subjects stood in front of a wide field-of-view screen, some subjects reported that they could see the ceiling. This would provide a visual reference that may have decreased ratings of vection intensity. Though subjective ratings of vection intensity were not different, cerebral activation was different with and without a fixation cross. This may indicate that the optic flow information was subconsciously perceived differently than verbally reported in healthy adults. An additional limitation of this study was that the presentation of the visual stimuli was not counterbalanced for fixation and no fixation conditions. This may have resulted in an order effect.

While optokinetic stimuli are often utilized by physical therapists during vestibular rehabilitation therapy, evidence-based stimulus parameters for delivery of optokinetic stimuli are not yet known. This work provides a beginning understanding of the mechanisms of cortical processing of optic flow information, which is a necessary first step in establishing optimal rehabilitation regimens. Greater cortical activation in the bilateral fronto-temporo-parietal lobes provides preliminary support for the use of a fixation cross during habituation to optic flow. It is not yet known if this holds true for individuals with complaints of visual vertigo, and warrants further investigation in this population. This may lead to standardized delivery of optic flow as a physical therapy intervention for individuals with visual vertigo, decreased variation in practice patterns, and improved patient outcomes.

3.5 CONCLUSION

In healthy subjects, cortical activation was greater when optic flow moving unidirectionally in the yaw plane was viewed with a fixation cross. With fixation, greater activation was seen in the bilateral fronto-temporo-parietal lobes. Future work should explore if this same cortical activation pattern is present in individuals with complaints of visual vertigo. Functional NIRS, a non-invasive neuroimaging modality, is appropriate for exploring the relationships among optic flow, perception of vection, standing balance, and cerebral activation.

4.0 USE OF NEAR-INFRARED SPECTROSCOPY TO EXAMINE CEREBRAL ACTIVATION DURING OPTIC FLOW IN SUBJECTS WITH AND WITHOUT COMPLAINTS OF VISUAL VERTIGO

Visual vertigo describes symptoms of dizziness, disorientation, and/or impaired balance induced by environments with conflicting visual and vestibular information or complex visual stimuli.(Bronstein, 1995) Individuals with vestibular disorders often report exacerbation of their symptoms in such environments, which can lead to avoidance behaviors resulting in activity limitations and participation restrictions.(Staab, 2012) Individuals with visual vertigo are highly visually dependent(A. Bronstein, 1995), giving greater weight to visual information for the maintenance of quiet stance. Additionally, these visually-dependent individuals may display increased postural sway with full-field visual motion stimuli.(Bronstein, 1995; Rábago & Wilken, 2011)

Optokinetic stimuli are a subtype of optic flow, which is the continual change of images on the retina that occurs from movement of the visual environment with respect to the subject. Studies using PET(Brandt et al., 1998) and fMRI(Kleinschmidt et al., 2002) during optokinetic stimuli viewed with fixation reveal a reciprocal visual-vestibular inhibitory pattern. Activation of the visual cortex co-occurs with deactivation of the parieto-insular vestibular cortex. This pattern may reflect sensory re-weighting of visual and vestibular afferent information for balance, in which the more reliable or dominant sensory input is given greater weight.(Brandt et

al., 1998) It is not known if individuals with visual vertigo respond to optokinetic stimuli in the same manner as healthy individuals, i.e., demonstrating reciprocal visual-vestibular inhibition.

When a sensory conflict is presented, sensory reweighting occurs.(Peterka & Loughlin, 2004) As exploratory aims to examine the sensory reweighting of individuals with visual vertigo compared to healthy individuals, manipulation of the support surface was used to degrade somatosensory information. Specific aims three and four examined the effect of standing on a fixed and sway-referenced surface on cerebral activation and postural sway during optic flow. Additionally, the effect of standing on a surface that changes from fixed to sway-referenced in a visually complex (stationary) environment was explored. This simulates activities of daily living such as going on escalators, which is one of the items in the Visual Vertigo Analogue Scale.

4.1 SPECIFIC AIMS AND HYPOTHESES

4.1.1 First (primary) specific aim

To examine the effect of single sine and sum of sines optic flow on cerebral activation in patients with complaints of visual vertigo and healthy adults. The hypotheses related to this specific aim were:

H1.1 Cerebral activation in the bilateral temporal and occipital lobes, as measured by fNIRS, will be greater in patients with complaints of visual vertigo than in healthy adults.

H1.2 Cerebral activation in the bilateral temporal and occipital lobes, as measured by fNIRS, will be greater during sum of sines than single sine optic flow.

4.1.2 Second (secondary) specific aim

To examine the effect of single sine and sum of sines optic flow on postural sway in patients with complaints of visual vertigo and healthy adults. The hypotheses related to this specific aim were:

H2.1 Postural sway, as measured by the RMS and NPL of COP movements, will be greater in patients with complaints of visual vertigo than in healthy adults.

H2.2 Postural sway, as measured by the RMS and NPL of COP movements, will be greater during sum of sines than single sine optic flow, though both groups will exhibit increased postural sway when viewing optic flow than a stationary stimulus.

4.1.3 Third (exploratory) specific aim

To examine the effect of standing on a fixed and sway-referenced surface on cerebral activation during optic flow in patients with complaints of visual vertigo and healthy adults. The hypotheses related to this specific aim were:

H3.1 Cerebral activation in the bilateral temporal and occipital lobes, as measured by fNIRS, will be greater in patients with complaints of visual vertigo than in healthy adults.

H3.2 Cerebral activation in the bilateral temporal and occipital lobes, as measured by fNIRS, will be greater standing on a sway-referenced than a fixed surface.

4.1.4 Fourth (exploratory) specific aim

To examine the effect of standing on a fixed and sway-referenced surface on postural sway during optic flow in patients with complaints of visual vertigo and healthy adults. The hypotheses related to this specific aim were:

H4.1 Postural sway, as measured by the RMS and NPL of COP movements, will be greater in patients with complaints of visual vertigo than in healthy adults.

H4.2 Postural sway, as measured by the RMS and NPL of COP movements, will be greater standing on a sway-referenced than a fixed surface.

4.2 METHODS

This experiment was performed in order to accomplish the specific aims described above. Patients with complaints of visual vertigo and healthy adults were exposed to optic flow while

cerebral activation and postural sway data were recorded (Figure 10). The support surface was either fixed or sway-referenced. All data were collected in the Medical Virtual Reality Center.

Figure 10. Experimental setup for study two. The subject stood on a force plate and was exposed to optic flow in a three-screen wide field of view virtual environment. Subjects wore an electromagnetic tracker on top of their head and on their back, and a NIRS head cap.

4.2.1 Study design

This study consisted of an ABABA design, where A was comprised of a stationary checkerboard and bullseye and B was comprised of anterior-posterior optic flow. This design provided two opportunities (B_1 and B_2 phases) to evaluate the effects of optic flow. Ten trials were conducted during a single experimental visit (Figure 11).

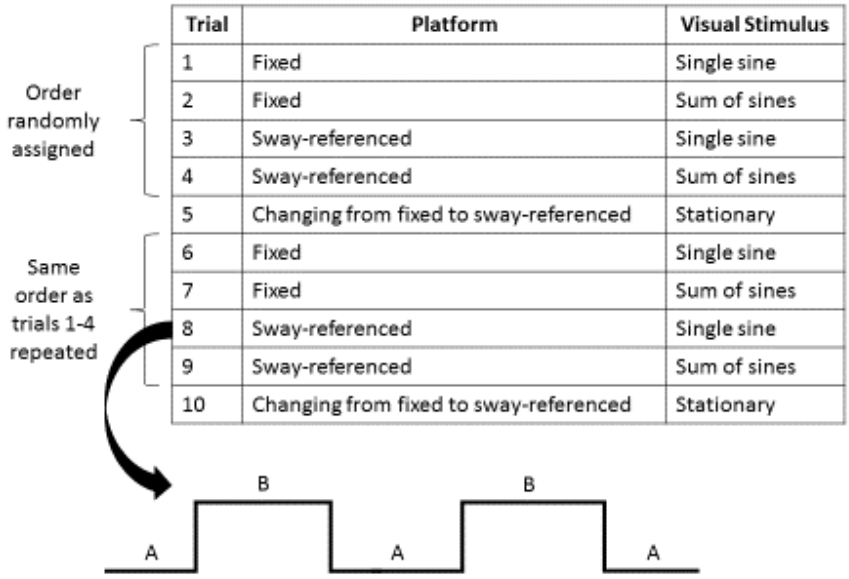


Figure 11. Experimental design for study two. The order of trials 1-4 was randomly assigned, and then the same order was repeated during trials 6-9. For each of the ten trials (depicted in the table), an ABABA design was used for viewing the visual stimulus. The visual stimulus had three stationary phases (A) and two optic flow phases (B). For example, during Trial 8 the subject stood on a sway-referenced platform while the visual stimulus changed from stationary to single sine anterior-posterior optic flow**.**

4.2.2 Inclusion criteria

Men and women between the ages of 18 and 65 were eligible to participate. All subjects were right-handed, as determined by the Edinburgh Handedness Inventory-Short Form.(Veale, 2014) While the original measure(Oldfield, 1971) had 10 items, the short form has 4 items (writing, throwing, using a toothbrush, and using a spoon). Both scales are strongly correlated (Spearman's $\rho = .90$) and have substantial agreement (kappa = .72).(Veale, 2014) Subjects were asked to abstain from alcohol for 48 hours before the experimental visits. Alcohol is known to

increase postural sway (Nieschalk et al., 1999), and thus would be a confounding factor in our study. In addition, subjects were asked to get a good night's sleep (7-8 hours) the night before testing. Sleep deprivation is known to negatively affect the postural stability of adults (Aguiar & Barela, 2014) and would, therefore, be a confounding factor in our study.

4.2.2.1 Inclusion criteria for healthy controls

Healthy men and women were eligible to participate as age- and gender-matched controls. They were matched based on self-report of gender and age within three years of the patient's age. Subjects were recruited from the University of Pittsburgh and surrounding area.

4.2.2.2 Inclusion criteria for patients with complaints of visual vertigo

Men and women with complaints of visual vertigo were eligible to participate. Patients were recruited from the clinical practices of a board-certified neurologist at the University of Pittsburgh.

Patients were determined to have complaints of visual vertigo by a board-certified neurologist. This diagnosis was determined based on the findings of the qualitative and quantitative examination, as well as the results of the Visual Vertigo Analogue Scale (VVAS). Patients were determined to have complaints of visual vertigo if they rated at least two of the nine items on the VVAS above zero (VVAS positive).(Dannenbaum, Chilingaryan, & Fung, 2011) The VVAS is used to rate the intensity of dizziness induced by daily situations (Appendix D). It is internally consistent and reliable (Cronbach's $\alpha = 0.94$) and moderately correlated with the Dizziness Handicap Inventory (DHI) ($r = 0.67$).(Dannenbaum, Chilingaryan, & Fung, 2011) Another study reported the correlation between the two measures as 0.54.(Grigol et al., 2015)

Patients also had to report a score of 31 or greater on the DHI, indicating a moderate handicap.(Whitney, Wrisley, Brown, & Furman, 2004) The DHI was developed to assess the handicapping impact of dizziness on daily life. It consists of 25 items in three domains (functional, emotional, and physical).(Jacobson & Newman, 1990) It is internally consistent and reliable (Cronbach's $\alpha = 0.89$).(Jacobson & Newman, 1990)

4.2.3 Exclusion criteria

4.2.3.1 Exclusion criteria for healthy controls

Subjects were ineligible to participate in the study if they had: a history of otologic or neurologic disease; history of migraine; corrected binocular vision worse than 20/40, macular degeneration, or glaucoma; results of screening tests that indicated vestibular asymmetry or loss; medication use that may affect balance (e.g., antipsychotics, barbiturates, benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants); unwillingness to abstain from alcohol for 48 hours prior to testing; known pregnancy; and/or body weight greater than 118 kilograms. A history of migraine was determined based on a previous diagnosis or as a result of a questionnaire asked during the phone screening interview (Appendix A).

4.2.3.2 Exclusion criteria for patients with complaints of visual vertigo

Patients were ineligible to participate in the study if their DHI score was less than or equal to 30, or if they did not complain of visual vertigo. Patients were also excluded if they had: corrected binocular vision worse than 20/40, macular degeneration, or glaucoma; unwillingness to abstain from alcohol for 48 hours prior to testing; known pregnancy; and/or body weight greater than 118 kilograms. Patients using medications that may affect balance (e.g., antipsychotics,

barbiturates, vestibular suppressants) or cerebral blood flow (e.g., triptans) were tested at least 48 hours after taking the last dose.

4.2.4 Power analysis

An a priori power analysis was conducted using G*Power to determine an appropriate sample size for a repeated measures analysis of variance (ANOVA) with a between-subjects factor. An effect size was estimated using Cohen's *d*, which was calculated as the T-score divided by the square root of the number of subjects. For the previous study described in Chapter 3.0, this was 0.99 for comparing the differences in brain activation between coherent and pseudo-randomly moving optic flow in healthy adults. Cohen's *d* was converted to *f* using an online calculator (http://www.psychometrica.de/effect_size.html). For two groups with ten measurements, with a 0.5 correlation among repeated measures (the default), when the effect size was set to 0.495, power was set to 0.80, and alpha was set to 0.05, a total sample size of 20 was indicated (10 subjects per group). Since the effect size in patients with complaints of visual vertigo is not known, a slightly larger sample of 15 subjects per group (n = 30) was used.

4.2.5 Optic flow stimulus

An anterior-posterior optic flow stimulus was selected to simulate the "moving room" paradigm used in previous research. The structure of the optic flow was designed so that the response of the visual-postural system would be maximal.(Stoffregen, 1985) The visual stimulus parameters replicated those used in a previous study investigating the effects of optic flow on postural control.(Sparto et al., 2006) It consisted of a checkerboard with alternating black and white

rectangles on the side screens to provide lamellar optic flow in the peripheral field of view; and bullseye pattern of alternating black and white rings on the front screen to provide radial optic flow in the central field of view. The checkerboard pattern appeared smaller in the distance to provide depth information (a perspective correction was applied). The luminance of the black and white areas was 1 and 170 candela/m^2, respectively. For anterior-posterior optic flow, there were two motion stimuli: single sine (frequency = 0.25 Hz; peak amplitude = 8 cm) and sum of sines (sum of three sines: frequency = $\pi/10$, $\pi/13$, $\pi/17$ Hz). Both stimuli had an RMS velocity of 8.88 degrees per second. The sum of three sines was used to produce changes in the velocity that would be difficult to anticipate.(Andersen & Dyre, 1989) The baseline (control) condition was a stationary checkerboard and bullseye. The visual stimulus was back-projected onto a three-screen wide field of view (180 degrees horizontal and 70 degrees vertical). Image height was adjusted so the center of the bullseye was at eye level. Subjects faced the front screen that was 1.5 meters away. As part of the ABABA design, each block was presented for 36 seconds for a total of 3 minutes for each trial.

4.2.6 Study protocol

This study was approved by the University of Pittsburgh Institutional Review Board (PRO16060053). Subjects provided informed consent at the start of the Screening Visit, before undergoing formal screening to determine if the inclusion and exclusion criteria were met. The screening for exclusion criteria consisted of demographic information, hand dominance, visual acuity testing, neurologic examination, subjective visual vertical testing (bucket test (Zwergal et al., 2009)), checking for cerumen, and tests for vestibular hypofunction. The tests for vestibular hypofunction were caloric testing, electronystagmography, and rotation testing. Vestibular

evoked myogenic potentials testing was not performed. It was decided that normal otolith function would be assumed if the subject reported no history or otologic or neurologic disease, caloric testing was normal, and if performance on the bucket test (10 trials) was normal. The bucket test is a simple bedside test for assessment of subjective visual vertical and has excellent inter-test (0.89-0.90) and intra-test (0.92) reliability.(Zwergal et al., 2009) Its clinical utility as a screening test, however, has been called into question.(Cohen & Sangi-Haghpeykar, 2012) While good cut-points on receiver operating characteristics analyses for differentiating normal subjects from those with unilateral hypofunction or benign paroxysmal positional vertigo could not be established with the bucket test, it was able to quantify the deviation in subjective visual vertical.(Cohen & Sangi-Haghpeykar, 2012) Thus, we used the bucket test as one part of the formal screening, and evaluated its results amongst all of the examination findings for determination of a subject's eligibility for inclusion in the study. In addition to this bedside test of SVV, patients also completed computerized SVV testing. Previous studies have found that patients with visual vertigo complaints have deficits with SVV testing, (Guerraz et al., 2001) and we wished to quantify the magnitude of this deficit if present.

The patients with complaints of visual vertigo completed four additional questionnaires during the Screening Visit to assess how personal and environmental factors influence their disability. The Hospital Anxiety and Depression Scale was used to identify and measure self-reported severity of anxiety and depression. This scale is reliable and valid for detecting and measuring the severity of these emotional disorders.(Zigmond & Snaith, 1983) Individuals with visual vertigo have more anxiety than individuals with vestibulopathy but without visual vertigo and healthy controls.(Zur et al., 2015) Anxiety-related gaze instability has been proposed as one possible pathophysiologic mechanism for visual vertigo.(Staab, 2014) Additionally, an anxious-

introverted personality may be a risk factor for development of chronic subjective dizziness.(Staab, Rohe, Eggers, & Shepard, 2014) The Vestibular Activities and Participation Measure was used to quantify the disabling effect of vestibular disorders on activities and participation according to the International Classification of Functioning, Disability and Health (ICF) framework.(Alghwiri et al., 2012) This measure has excellent test-retest reliability (ICC = 0.95) and is strongly correlated with the DHI total score ($\rho = 0.74$).(Alghwiri et al., 2012) The ICF Vestibular Environmental Scale was used to identify environmental triggers of dizziness according to the ICF framework.(Whitney et al., 2016) The number of environmental triggers is correlated with the DHI total score ($\rho = 0.47$).(Whitney et al., 2016) The three items (design of buildings, crowds, and quick movements in the vicinity) that were the most frequently reported by individuals with vestibular disorders involve complex or moving visual stimuli.(Whitney et al., 2016) Patients had the option of completing the Vestibular Activities Avoidance Instrument, which is being developed as new self-reported outcome measure to identify individuals with vestibular and balance disorders who may avoid activities.(Alshebber et al.)

There was only one experimental visit. Ten trials were conducted, and the order of the first four trials was randomized using the Research Randomizer (https://www.randomizer.org/) internet program to decrease practice and fatigue effects. This same order was used for trials 6-9. To investigate the exploratory specific aims, two additional trials in which the platform changed from fixed to sway-referenced while the visual surround remained stationary (the baseline condition) were included as trials 5 and 10. During sway-referenced trials the platform rotated about an axis collinear with the ankles, such that body sway and platform motion were directly proportional. Optic flow moved independently of the sway-referenced platform. Allocation concealment was preserved by keeping the random assignments in paper envelopes

until the start of the experimental visit. During all of the trials the subject was instructed to: "Look straight ahead in a relaxed manner at the bullseye pattern." Subjects stood in stocking feet, with feet shoulder-width apart. A safety harness that was tethered to the ceiling was worn. The tether was not so tight that it would hinder postural sway or provide additional sensory feedback to the subject. Subjects were given a 5 minute seated rest break between trials to decrease fatigue and carryover effects.

Before the first trial, after every optic flow trial, and 10 minutes after the last trial, the subjects were asked to verbally rate their discomfort using the Subjective Units of Discomfort (SUD) measure (0-100 range).(Wolpe, 1982) Additionally, the Simulator Sickness Questionnaire (SSQ) was used to monitor symptoms.(Kennedy, Lane, Berbaum, & Lilienthal, 1993) The SSQ is comprised of 16 items, and uses a 0 to 3 scale to rate symptom severity (0 = none, 1 = slight, 2 = moderate, 3 = severe). There are three subscales: nausea, oculomotor, and disorientation. For these subscales, the sum of the ratings is multiplied by the appropriate weight (9.54 for nausea, 7.58 for oculomotor, and 13.92 for disorientation) to obtain a weighted total.(Kennedy et al., 1993) For the total score, the sum of all the ratings is multiplied by 3.74.(Kennedy et al., 1993) Subjects with vestibular disorders endorse more non-zero responses on the SUD, greater average SUD ratings, and greater oculomotor and disorientation subscale scores on the SSQ than healthy controls during optic flow in a virtual reality environment.(Whitney, Sparto, Cook, Redfern, & Furman, 2013) Healthy subjects also endorse more non-zero responses on the SUD and SSQ during the first visit than during subsequent visits to a virtual reality grocery store.(Sparto, Whitney, Hodges, Furman, & Redfern, 2004)

4.2.7 Outcome measures

Cerebral activation was measured using the NIRS head cap. Postural sway was measured using a force plate and electromagnetic tracking system. Each of these outcome measures was the same as described in sections 3.2.6.1 and 3.2.6.4 of the previous study.

4.2.8 Statistical analyses

Data were analyzed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY) and MATLAB (Mathworks, Natick, MA). Demographic characteristics were compared between the two groups using dependent *t*-tests for continuous variables.

4.2.8.1 Near-infrared spectroscopy

NIRS data were analyzed based on a general linear model with a boxcar function of the timing and duration of the optic flow as a regressor. First, MATLAB was used to pre-process the data. This involved marking the onset of the optic flow phases during the trials. Following pre-processing, the optical data was down sampled from 20 Hz to 4 Hz using a custom-built MATLAB-based acquisition software program.(Barker et al., 2013) Optical data recorded as changes in light intensity as a function of time was converted to optical density. The modified Beer-Lambert law was applied to convert the data from optical density to concentration change.(Cope et al., 1988) A partial path length correction of 0.1 (differential path length factor = 6 and partial volume factor = 60) was used.(Strangman et al., 2003) The time-course of hemoglobin changes for each source-detector pair was analyzed using a general linear model,

where β is the coefficient (weight) of the optic flow stimulus condition for the source-detector channel.

To reduce effects of motion artifacts and systemic physiology, an iteratively auto-regressively whitened, weighted least squares model was used.(Barker et al., 2013) This regression model uses and n^{th} order auto-regressive filter determined by an Akaike model-order selection to whiten both sides of the general linear model equation. Basically, an iterative procedure is used to whiten serially correlated noise and reweight statistical outliers using a robust regression procedure using a bi-square weighting function. This reweighting reduces the impact of motion-artifacts since these points are generally statistical outliers from a normal distribution following auto-regressive whitening. Using this model, the regression coefficients and their error-covariance (Covβ) are estimated, which is used to define statistical tests between optic flow stimulus conditions. The subject-level statistical analysis investigated if the optic flow stimulus elicited a significant brain activation compared with the stationary visual stimulus. The regression model was solved sequentially for each data file for each of the 30 subjects. All source-detector pairs within a file were solved concurrently, yielding a full covariance model of the noise, which was used in the group-level analysis. T-tests were conducted to determine if the regression coefficients were statistically non-zero.

Group-level statistical analysis was performed using a linear mixed-effects model, using the task-related regression coefficients from the subject-level general linear model as the dependent variable and subject included as a random effect. A modified version of the MATLAB function fitLME (linear mixed effects model estimator) was used to solve the weighted maximum likelihood estimate of the parameters. The model was whitened using the error-covariance from the subject-level general linear model. A false discovery rate

correction(Benjamini & Hochberg, 1995) was applied to control for Type I error, with the significance level set at 0.05 ($q \leq 0.05$). The group-level statistical analysis investigated the effect of single sine versus sum of sines optic flow using a linear mixed-effects model with optic flow condition as the fixed effect and subjects as a random effect. An ANOVA with group and surface condition included as random effects was used to determine if cerebral activation was different during single sine and sum of sines optic flow.

The spatial arrangement of detectors on the scalp was used to approximate the location of cerebral activity.(Boas et al., 2004) The location of the sources and detectors was registered to an anatomical MRI head Colin27 atlas(Holmes et al., 1998) using an affine registration algorithm.(Abdelnour & Huppert, 2009) This registration and a finite-element model of light diffusion was used to build a forward model to describe the sensitivity of the head cap to underlying brain regions.(Abdelnour & Huppert, 2009) Six regions of interest were explored (right and left anterior and posterior temporal, and right and left occipital lobes). Then, image reconstruction was performed based on a model that used wavelets to model the surface of the cerebral cortex.(Abdelnour et al., 2009) A group-level image was reconstructed that best modeled all of the subjects' data.

4.2.8.2 Postural sway

Anterior-posterior and medial-lateral translation data from the electromagnetic trackers on the head and hips were digitally low-pass filtered using zero-phase implementation of a fourth order Butterworth filter with a cutoff frequency of 2 Hz. Filtered data was then used to calculate the RMS and NPL of the anterior-posterior and medial-lateral movement of the head and hips.

Data from the force plate was post-processed using MATLAB to obtain COP measures. The COP was digitally low-pass filtered and zero-meaned. Low-pass filtering was achieved

through zero-phase implementation of a fourth order Butterworth filter with a cutoff frequency of 2 Hz. Filtered data was then used to calculate the RMS and NPL of the anterior-posterior and medial-lateral movement of the COP.

This data was checked for normality using the Shapiro-Wilk test in addition to examination of the histograms, q-q plots, box plots, skewness, and kurtosis. If the *p*-value for the Shapiro-Wilk test was greater than .05, the data were normally distributed. Very few of the dependent variables were normally distributed, but Linear Mixed-Effects Models are robust to violations of normality and so were still used to test how the main effect of optic flow stimulus contributed to observations of postural sway.

Differences between groups (patients versus controls), surface and optic flow conditions (fixed floor/single sine, fixed floor/sum of sines, sway-referenced floor/single sine, sway-referenced floor/sum of sines) and visual stimuli periods (optic flow versus stationary surround) were examined using linear mixed-effects models. In total, twelve models were estimated: anterior-posterior head NPL, anterior-posterior head RMS, medial-lateral head NPL, medial-lateral head RMS, anterior-posterior hips NPL, anterior-posterior hips RMS, medial-lateral hips NPL, medial-lateral hips RMS, anterior-posterior COP NPL, anterior-posterior COP RMS, medial-lateral COP NPL, and medial-lateral COP RMS. The AIC and BIC were used to select a model with the most appropriate covariance structure. Unstructured, compound symmetry, compound symmetry heterogeneous, first-order autoregressive heterogeneous, and Toeplitz heterogeneous were all explored. Using a compound symmetry heterogeneous covariance structure, the models converged and had acceptable AIC and BIC values. A restricted maximum likelihood approach was used.

Differences between groups (patients versus controls) and periods (sway-referenced floor versus fixed floor) were examined using linear mixed-effects models for the changing from a fixed floor to a sway-referenced floor with a stationary surround condition. In total, twelve models were estimated: anterior-posterior head NPL, anterior-posterior head RMS, medial-lateral head NPL, medial-lateral head RMS, anterior-posterior hips NPL, anterior-posterior hips RMS, medial-lateral hips NPL, medial-lateral hips RMS, anterior-posterior COP NPL, anterior-posterior COP RMS, medial-lateral COP NPL, and medial-lateral COP RMS. The AIC and BIC were used to select a model with the most appropriate covariance structure. Unstructured, compound symmetry, compound symmetry heterogeneous, first-order autoregressive heterogeneous, and Toeplitz heterogeneous were all explored, but no models converged using these covariance structures. Using a Toeplitz covariance structure, the model converged and had acceptable AIC and BIC values. A restricted maximum likelihood approach was used.

As the findings were consistent for the visual stimuli periods (three stationary and two optic flow) and condition (first and second trial of the same condition, e.g. fixed floor with sum of sines optic flow observed second and seventh during ten trials), the mean values for the dependent variables were combined for period and condition to reduce the number of variables. The three stationary visual stimuli periods were pooled into one stationary visual stimuli variable. The two optic flow visual stimuli periods were pooled into one optic flow visual stimuli variable. Repetitions of trials for the same conditions were pooled together, reducing eight conditions into four conditions. Similarly, the two repetitions of the fixed floor changing to sway-referenced floor conditions were pooled together, reducing two conditions into one condition. The fixed effects were group (patients with visual vertigo versus healthy controls), surface and optic flow conditions, and period (optic flow versus stationary visual field), and the

interaction effects were group by condition, group by period, and condition by period. Subject was included as a random effect. Post-hoc testing consisted of pairwise comparisons based on the estimated marginal means. The significance level was set at $\alpha = 0.05$.

4.3 RESULTS

Forty subjects were recruited and screened for inclusion in the study. In the patient group, three patients were excluded due to DHI scores less than or equal to 31, and one patient withdrew from the study after seeing the optic flow stimulus because it was too provocative. In the control group, five individuals were disqualified from participating based on the exclusion criteria (one was a non-native English speaker, two had strabismus, one had a reduced vestibular response, and one was a mixed hander). One healthy individual who was eligible to participate was withdrawn because she was unable to stand on the sway-referenced surface.

There were 10 females and 5 males in each group. There was no difference in the ages of the patients and healthy controls, $t(14) = 1.871$, $p = 0.082$. The mean age of the patients was 39 (SD 12, range 25-61) and the mean age of the healthy controls was 38 (SD 12, range 24-61). The mean height of the patients was 169 cm (SD 7, range 157-178) and the mean height of the healthy controls was 172 cm (SD 9, range 152-185). The heights of the groups was not different, $t(14) = -1.329$, $p = 0.205$. The mean weight of the patients was 69 kg (SD 12, range 53-100) and the mean weight of the healthy controls was 77 kg (SD 17, range 49-105). The weights of the groups was not different, $t(14) = -1.852$, $p = 0.085$.

All participants were right handed. The frequency of laterality quotient scores is presented in Table 4. While the median was 100 for both groups, the mean laterality quotient was 89 for the patients (SD 14, range 63-100) and 99 (SD 3, range 88-100) for the healthy controls. As the laterality quotient for both groups was not normally distributed, a Wilcoxon Signed Ranks test revealed that the handedness of the groups was different, $Z = -2.220$, $p = 0.026$. There was no difference in education level (defined as the highest level of schooling completed) between the groups, $t(14) = -0.926$, $p = 0.37$.

Table 4. Frequency of laterality quotient scores on the Edinburgh Handedness Inventory-Short Form for both the visual vertigo and control groups.

Laterality Quotient Score	Patients (n = 15)	Healthy Controls (n = 15)
63	2	0
75	2	0
88	3	1
100	8	14

The patients were diagnosed by a board-certified neurologist as having a variety of central and/or peripheral vestibular disorders (Table 5). The most common diagnosis was vestibular migraine, possibly affecting up to 40% of the patient group. In some cases (n = 3), the patient presented with dizziness of an uncertain etiology.

Table 5. Diagnoses of individuals in the patient group.

Patient Number (n = 15)	Diagnoses
1	Vestibular migraine
2	Dizziness of uncertain etiology; visual motion sensitivity
3	Vestibular migraine
4	Right peripheral vestibulopathy; motion discomfort; possible vestibular migraine
5	Endolymphatic hydrops (uncertain laterality)
6	Dizziness of uncertain etiology
7	Combination of vestibular migraine, anxiety disorder, and a peripheral vestibulopathy (migraine-anxiety-related dizziness with a peripheral component)
8	Dizziness of uncertain etiology (possible vestibular migraine)
9	Post-concussion dizziness with vestibulospinal findings on posturography (no evidence of labyrinthine concussion)
10	Right Meniere's disease
11	Post-traumatic benign positional vertigo variant
12	Persistent postural-perceptual dizziness
13	Vestibular migraine with a peripheral component
14	Right labyrinthine concussion; visual vertigo
15	Right peripheral vestibulopathy of uncertain etiology

Selected for their complaints of visual vertigo, the patients reported a mean score of 58 for both the modified VVAS and the new six exploratory items of the VVAS (VVAS1 and VVAS2 in Table 6, respectively). Their mean score on the DHI was 49 (SD 16). The scores for the emotional, functional, and physical domains of the DHI were similar (see Table 6); repeated measures ANOVA, $F(2,28) = 0.149$, $p = 0.863$. A cut off score of 8 on the Hospital Anxiety and Depression Scale was used to identify cases of anxiety and depression.(Bjelland, Dahl, Haug, &

Neckelmann, 2002) Six patients were depressed and 14 were anxious. In the control group, no patients were depressed and only 2 were anxious. Depression and anxiety scores differed between the two groups. As the depression scores for the healthy controls was not normally distributed, a Wilcoxon Signed Ranks test revealed that the patients were more depressed than the healthy controls, Z = -3.068, p =0.002. The patients were more anxious than the healthy controls, $t(14) = 4.520$, $p < 0.001$.

Table 6. Self-reported outcome measures for both the visual vertigo and control groups. Values represent the mean (standard deviation). VVAS1 = Visual Vertigo Analogue Scale (original items); VVAS2 = Visual Vertigo Analogue Scale (exploratory items); DHI = Dizziness Handicap Inventory; DHI-E = Emotional domain of the DHI; DHI-F = Functional domain of the DHI; DHI-P = Physical domain of the DHI; HADS-D = Hospital Anxiety and Depression Scale depression score; HADS-A = Hospital Anxiety and Depression Scale anxiety score; * indicates $p \leq 0.05$.

Group	VVAS1	VVAS2	DHI	DHI-E	DHI-F	DHI-P	HADS-D	HADS-A
Patients	58 (21)	59 (23)	49 (16)	16 (7)	16 (6)	17 (6)	6 (4)*	12 (5)*
Controls	-	-	-	-	-	-	1 (1)*	4 (3)*

4.3.1.1 Near-infrared spectroscopy

Statistical analyses using a general linear model revealed significant activation in the regions of interest in both the patients and the healthy controls in response to the visual and platform conditions. The changes observed in the patients and the healthy controls are described below for the five testing conditions.

Fixed Floor - Single Sine Optic Flow

In patients, during the single sine optic flow while standing on a fixed floor, there were no significant differences in cerebral activation between the optic flow and stationary visual stimuli periods (Table 7). In the healthy controls, increased HbO_2 was seen in the left anterior temporal region (T = 4.10, $p < .001$, FDR-corrected). A decrease in Hb was seen in the left

posterior temporal region (T = -2.39, p = .021, FDR-corrected). Increased HbO_2 and decreased Hb was seen in the right anterior temporal region (T = 4.35, p < .0001, FDR-corrected for HbO_2; T = -1.97, p = .049, FDR-corrected for Hb). A decrease in Hb was seen in the right posterior temporal region (T = -2.35, p = .022, FDR-corrected). Healthy controls only displayed a significant increase in HbO_2 in the right occipital region (T = 2.10, p = .037, FDR-corrected), though the left occipital region showed a similar trend.

Table 7. Change in cerebral activation when viewing single sine optic flow while standing on a fixed surface. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Group	Region of Interest	Chromo-phore	Beta	Standard Error	T	*p*	*q*
Patients	Left anterior temporal	HbO_2	-0.88	0.50	-1.77	0.08	0.64
		Hb	-0.07	0.34	-0.21	0.84	0.88
	Left posterior temporal	HbO_2	1.08	0.70	1.53	0.13	0.11
		Hb	-0.18	0.55	-0.32	0.75	0.42
	Right anterior temporal	HbO_2	-0.91	0.47	-1.93	0.05	0.05
		Hb	0.21	0.44	0.47	0.64	0.37
	Right posterior temporal	HbO_2	-0.20	0.71	-0.28	0.78	0.44
		Hb	-0.65	0.62	-1.05	0.30	0.21
	Left occipital	HbO_2	1.13	0.58	1.94	0.05	0.05
		Hb	0.01	0.43	0.03	0.97	0.50
	Right occipital	HbO_2	0.39	0.55	0.71	0.48	0.31
		Hb	0.23	0.43	0.53	0.59	0.36
Healthy Controls	Left anterior temporal	HbO_2	1.65	0.40	4.11	< 0.001	< 0.001*
		Hb	0.12	0.29	0.43	0.67	0.39
	Left posterior temporal	HbO_2	0.19	0.80	0.23	0.82	0.44
		Hb	-1.27	0.53	-2.39	0.02	0.02*
	Right anterior temporal	HbO_2	2.53	0.58	4.35	< 0.001	< 0.001*
		Hb	-0.87	0.44	-1.97	0.05	0.05*
	Right posterior temporal	HbO_2	0.26	0.68	0.38	0.71	0.40
		Hb	-1.39	0.59	-2.35	0.02	0.02*
	Left occipital	HbO_2	0.99	0.52	1.92	0.06	0.05
		Hb	0.28	0.41	0.69	0.49	0.31
	Right occipital	HbO_2	1.37	0.65	2.10	0.04	0.04*
		Hb	-0.48	0.47	-1.03	0.31	0.21

Fixed Floor – Sum of Sines Optic Flow

In patients, during the sum of sines optic flow while standing on a fixed floor, decreased HbO_2 and decreased Hb was seen in the left anterior temporal region (T = -2.89, p = .006, FDR-corrected for HbO_2; T = -2.96, p = .005, FDR-corrected for Hb). Increased HbO_2 and decreased Hb was seen in the left posterior temporal region (T = 3.24, p = .002, FDR-corrected for HbO_2; T = -3.66, p < .001, FDR-corrected for Hb). Increased HbO_2 was seen in the right occipital region of interest (T = 2.32, p = .023, FDR-corrected), though the left occipital region showed a similar trend (Table 8). The healthy controls displayed an increase in HbO_2 in the bilateral anterior temporal regions (T = 2.32, p =.023, FDR-corrected for left; T = 3.25, p = .002, FDR-corrected for right); a decrease in Hb in the left posterior temporal region (T = -2.42, p = .020, FDR-corrected); and an increase in HbO_2 in both occipital regions (T = 2.35, p = .022, FDR-corrected for left; T = 3.08, p = .003, FDR-corrected for right).

Table 8. Change in cerebral activation when viewing sum of sines optic flow while standing on a fixed surface. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Group	Region of Interest	Chromo-phore	Beta	Standard Error	T	*p*	*q*
Patients	Left anterior temporal	HbO_2	-1.55	0.54	-2.89	< 0.01	0.01*
		Hb	-1.02	0.34	-2.96	< 0.01	0.01*
	Left posterior temporal	HbO_2	2.78	0.86	3.24	< 0.01	< 0.01*
		Hb	-2.18	0.60	-3.66	< 0.001	< 0.001*
	Right anterior temporal	HbO_2	-0.68	0.54	-1.26	0.21	0.16
		Hb	-0.28	0.44	-0.64	0.52	0.32
	Right posterior temporal	HbO_2	0.87	0.77	1.14	0.26	0.19
		Hb	-0.39	0.66	-0.59	0.55	0.34
	Left occipital	HbO_2	1.01	0.58	1.74	0.08	0.08
		Hb	0.50	0.42	1.18	0.24	0.18
	Right occipital	HbO_2	1.35	0.58	2.32	0.02	0.02*
		Hb	0.23	0.44	0.53	0.59	0.36
Healthy Controls	Left anterior temporal	HbO_2	0.96	0.41	2.32	0.02	0.02*
		Hb	-0.08	0.31	-0.25	0.80	0.44
	Left posterior temporal	HbO_2	1.03	0.76	1.35	0.18	0.14
		Hb	-1.27	0.52	-2.42	0.02	0.02*
	Right anterior temporal	HbO_2	1.66	0.51	3.25	< 0.01	< 0.01*
		Hb	-0.20	0.43	-0.47	0.64	0.37
	Right posterior temporal	HbO_2	0.73	0.67	1.08	0.28	0.20
		Hb	-0.82	0.55	-1.49	0.14	0.12
	Left occipital	HbO_2	1.20	0.51	2.35	0.02	0.02*
		Hb	-0.30	0.41	-0.74	0.46	0.30
	Right occipital	HbO_2	1.79	0.58	3.08	< 0.01	< 0.01*
		Hb	-0.50	0.46	-1.08	0.28	0.20

Sway-referenced Floor - Single Sine Optic Flow

In patients, during the single sine optic flow while standing on a sway-referenced floor, increased HbO_2 and decreased Hb was seen in the left anterior temporal region (T = 4.53, p < .001, FDR-corrected for HbO_2; T = -4.64. p < .001, FDR-corrected for Hb) and in the left posterior temporal region (T = 4.60, p < .001, FDR-corrected for HbO_2; T = -5.31, p < .001, FDR-corrected for Hb). This was similar to the decreased Hb seen in the right anterior temporal (T = -5.84, p < .001, FDR-corrected) and the increased HBO_2 and decreased Hb seen in the right posterior temporal (T= 7.42, p < .001, FDR-corrected for HbO_2; T = -5.76, p < .001, FDR-corrected for Hb) regions. Increased HbO_2 was seen in both occipital regions of interest (T = 2.36, p = .021, FDR-corrected for left; T = 2.40, p = .021, FDR-corrected for right). A similar pattern of activation was seen in the healthy controls for all regions of interest (Table 9). Increased HbO_2 was seen in left anterior temporal region (T = 4.53, p < .001, FDR-corrected). Increased HbO_2 and decreased Hb was seen in the left posterior temporal region (T = 3.11, p = .003, FDR-corrected for HbO_2; T = -3.40, p = .001, FDR-corrected) and in the right anterior (T = 4.25, p < .001, FDR-corrected for HbO_2; T = -2.70, p = .010, FDR-corrected) and the posterior temporal regions (T = 6.64, p < .001, FDR-corrected for HbO_2; T = -2.59, p = 0.013, FDR-corrected for Hb) in healthy adults. The healthy controls displayed a significant increase in HbO_2 in the bilateral occipital regions (T = 3.21, p = .002, FDR-corrected for left; T = 2.38, p = .021, FDR-corrected for right).

Table 9. Change in cerebral activation when viewing single sine optic flow while standing on a sway-referenced surface. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Group	Region of Interest	Chromo-phore	Beta	Standard Error	T	*p*	*q*
Patients	Left anterior temporal	HbO_2	2.24	0.49	4.053	< 0.001	< 0.001*
		Hb	-1.60	0.35	-4.64	< 0.001	< 0.001*
	Left posterior temporal	HbO_2	3.85	0.84	4.60	< 0.001	< 0.001*
		Hb	-3.15	0.59	-5.31	< 0.001	< 0.001*
	Right anterior temporal	HbO_2	0.92	0.53	1.72	0.09	0.08
		Hb	-2.65	0.45	-5.84	< 0.001	< 0.001*
	Right posterior temporal	HbO_2	5.14	0.69	7.42	< 0.001	< 0.001*
		Hb	-3.60	0.63	-5.76	< 0.001	< 0.001*
	Left occipital	HbO_2	1.41	0.60	2.36	0.02	0.02*
		Hb	-0.44	0.42	-1.06	0.29	0.21
	Right occipital	HbO_2	1.30	0.54	2.40	0.02	0.02*
		Hb	-0.35	0.43	-0.81	0.42	0.27
Healthy Controls	Left anterior temporal	HbO_2	1.92	0.42	4.53	< 0.001	< 0.001*
		Hb	-0.37	0.29	-1.30	0.19	0.15
	Left posterior temporal	HbO_2	2.21	0.71	3.11	< 0.01	< 0.01*
		Hb	-1.74	0.51	-3.40	< 0.001	< 0.01*
	Right anterior temporal	HbO_2	2.32	0.55	4.25	< 0.001	< 0.001*
		Hb	-1.13	0.42	-2.70	< 0.01	0.01*
	Right posterior temporal	HbO_2	4.79	0.72	6.64	< 0.001	< 0.001*
		Hb	-1.44	0.56	-2.59	0.01	0.01*
	Left occipital	HbO_2	1.72	0.54	3.21	< 0.01	< 0.01*
		Hb	-0.55	0.42	-1.31	0.19	0.15
	Right occipital	HbO_2	1.62	0.68	2.38	0.02	0.02*
		Hb	-0.40	0.46	-0.88	0.38	0.25

Sway-referenced Floor – Sum of Sines Optic Flow

In patients, during the sum of sines optic flow while standing on a sway-referenced floor, increased activation was seen in the bilateral temporal regions of interest (Table 10). Increased HbO_2 and decreased Hb was seen in the left anterior temporal region (T = -1.54.185, $p < .001$, FDR-corrected for HbO2; T = -2.28, $p = .024$, FDR-corrected for Hb), left posterior temporal region (T = 3.96, $p < .001$, FDR-corrected for HbO_2; T = -3.54, $p < .001$, FDR-corrected for Hb), right anterior temporal region (T = 3.74, $p < .001$, FDR-corrected for HbO_2; T = -3.50, $p = .001$, FDR-corrected for Hb), and right posterior temporal region (T = 5.28, $p < .001$, FDR-corrected for HbO_2; T = -2.67, $p = .011$, FDR-corrected for Hb). Increased HbO_2 was only seen in the right occipital region of interest (T = 3.87, $p < .001$, FDR-corrected). In the healthy controls, increased activation was also seen in the bilateral temporal regions of interest. Increased HbO_2 and decreased Hb was seen in the left anterior temporal region (T = 8.04, $p < .001$, FDR-corrected for HbO_2; T = -3.63, $p < .001$, FDR-corrected for Hb), left posterior temporal region (T = 2.88, $p = .006$, FDR-corrected for HbO_2; T = -4.07, $p < .001$, FDR-corrected for Hb), right anterior temporal region (T = 8.61, $p < .001$, FDR-corrected for HbO_2; T = -7.51 $p < .001$, FDR-corrected for Hb), and right posterior temporal region (T = 8.20, $p < .001$, FDR-corrected for HbO_2; T = -4.21, $p < .001$, FDR-corrected for Hb). Increased HbO_2 was seen in both occipital regions of interest (T = 3.19, $p = .003$, FDR-corrected for left; T = 3.77, $p < .001$, FDR-corrected for right).

Table 10. Change in cerebral activation when viewing sum of sines optic flow while standing on a sway-referenced surface. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Group	Region of Interest	Chromo-phore	Beta	Standard Error	T	*p*	*q*
Patients	Left anterior temporal	HbO_2	1.99	0.48	4.16	< 0.001	< 0.001*
		Hb	-0.78	0.34	-2.27	0.02	0.02*
	Left posterior temporal	HbO_2	2.95	0.75	3.96	< 0.001	< 0.001*
		Hb	-2.13	0.60	-3.54	< 0.001	0.001*
	Right anterior temporal	HbO_2	1.85	0.49	3.74	< 0.001	< 0.001*
		Hb	-1.52	0.43	-3.50	0.001	0.001*
	Right posterior temporal	HbO_2	3.77	0.71	5.28	< 0.001	< 0.001*
		Hb	-1.70	0.64	-2.67	0.01	0.01*
	Left occipital	HbO_2	0.58	0.57	1.01	0.31	0.21
		Hb	0.02	0.45	0.04	0.97	0.50
	Right occipital	HbO_2	2.38	0.61	3.87	< 0.001	< 0.001*
		Hb	-0.08	0.44	-0.18	0.86	0.45
Healthy Controls	Left anterior temporal	HbO_2	3.31	0.41	8.04	< 0.001	< 0.001*
		Hb	-1.06	0.29	-3.63	< 0.001	0.001*
	Left posterior temporal	HbO_2	2.07	0.72	2.88	< 0.01	0.01*
		Hb	-2.16	0.53	-4.07	< 0.001	< 0.001*
	Right anterior temporal	HbO_2	4.96	0.58	8.61	< 0.001	< 0.001*
		Hb	-3.24	0.43	-7.51	< 0.001	< 0.001*
	Right posterior temporal	HbO_2	5.81	0.71	8.20	< 0.001	< 0.001*
		Hb	-2.39	0.57	-4.21	< 0.001	< 0.001*
	Left occipital	HbO_2	1.63	0.51	3.19	< 0.01	< 0.01*
		Hb	-0.29	0.43	-0.68	0.49	0.31
	Right occipital	HbO_2	2.14	0.57	3.77	< 0.001	< 0.001*
		Hb	0.01	0.47	0.01	0.99	0.51

Fixed Changing to Sway-referenced Floor – Stationary Surround

When patients viewed a stationary visual stimulus, but stood on a platform that changed from fixed to sway-referenced, increased HbO_2 and decreased Hb was seen in the left anterior temporal region (T = 2.42, p = .020, FDR-corrected for HbO_2; T = -2.00, p = .047, FDR-corrected for Hb). Decreased Hb was seen in the left posterior temporal region (T = -2.44, p = .020, FDR-corrected). In the right posterior temporal region, increased HbO_2 and decreased Hb was seen (T = 6.11, p < .001, FDR-corrected for HbO_2; T = -4.34, p < .001, FDR-corrected for Hb). No significant changes were seen in the occipital regions of interest (Table 11). In the healthy controls, increased HbO_2 was seen in the left anterior temporal region (T = 2.84, p = .007, FDR-corrected). Increased HbO_2 and decreased Hb was seen in the left posterior temporal region (T = 3.60, p < .001, FDR-corrected for HbO_2; T = -4.37, p < .001, FDR-corrected for Hb). Increased HbO_2 was seen in the right anterior temporal region (T = 3.79, p < .001, FDR-corrected) and decreased Hb was seen in the right posterior temporal region (T = -2.25, p = .026, FDR-corrected). Again, no significant changes were seen in the occipital regions of interest (see Table 11).

Table 11. Change in cerebral activation when viewing a stationary visual field while standing on a platform that changed from fixed to sway-referenced. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Group	Region of Interest	Chromo-phore	Beta	Standard Error	T	*p*	*q*
Patients	Left anterior temporal	HbO_2	1.26	0.52	2.42	0.02	0.02*
		Hb	-0.69	0.35	-2.00	0.05	0.05*
	Left posterior temporal	HbO_2	1.11	0.83	1.34	0.18	0.15
		Hb	-1.44	0.59	-2.44	0.02	0.02*
	Right anterior temporal	HbO_2	0.81	0.52	1.57	0.12	0.10
		Hb	-0.56	0.44	-1.27	0.20	0.15
	Right posterior temporal	HbO_2	4.50	0.74	6.11	< 0.001	< 0.001*
		Hb	-2.94	0.68	-4.34	< 0.001	< 0.001*
	Left occipital	HbO_2	0.89	0.68	1.30	0.19	0.15
		Hb	-0.12	0.46	-0.26	0.80	0.44
	Right occipital	HbO_2	0.50	0.62	0.81	0.42	0.27
		Hb	-0.45	0.47	-0.97	0.33	0.22
Healthy Controls	Left anterior temporal	HbO_2	1.11	0.39	2.84	< 0.01	0.01*
		Hb	-0.12	0.31	-0.38	0.70	0.40
	Left posterior temporal	HbO_2	2.22	0.62	3.60	< 0.001	< 0.001*
		Hb	-2.35	0.54	-4.37	< 0.001	< 0.001*
	Right anterior temporal	HbO_2	1.87	0.49	3.79	< 0.001	< 0.001*
		Hb	0.10	0.39	0.26	0.80	0.44
	Right posterior temporal	HbO_2	0.96	0.69	1.40	0.16	0.13
		Hb	-1.34	0.60	-2.25	0.03	0.03*
	Left occipital	HbO_2	0.84	0.50	1.69	0.09	0.08
		Hb	0.57	0.41	1.39	0.17	0.14
	Right occipital	HbO_2	0.47	0.55	0.84	0.40	0.26
		Hb	0.04	0.44	0.10	0.92	0.49

Patients versus Controls: Fixed Floor

Statistical analyses using a linear mixed-effects model revealed significantly less activation in the bilateral anterior temporal regions in the patients with complaints of visual vertigo in comparison to the healthy controls when standing on a fixed surface. During single sine optic flow while standing on a fixed surface, there was decreased HbO_2 in the bilateral anterior temporal regions in the patients in comparison to the healthy controls ($T = -3.95$, $p = .002$, FDR-corrected for left; $T = -4.59$, $p < .001$, FDR- corrected for right) (Table 12). Similarly, during sum of sines optic flow while standing on a fixed surface, there was decreased HbO_2 in the bilateral anterior temporal regions in the patients in comparison to the healthy controls ($T = -3.71$, $p = .004$, FDR-corrected for left; $T = -3.16$, $p = .018$, FDR-corrected for right) (Table 13).

Patients versus Controls: Sway-referenced Floor

During single sine optic flow while standing on a sway-referenced surface, there was no difference in the cortical activation between the patients and healthy controls (Table 14). During sum of sines optic flow while standing on a sway-referenced surface, there was decreased HbO_2 and increased Hb in the right anterior temporal region in the patients in comparison to the healthy controls ($T = -4.10$, $p = .002$, FDR-corrected for HbO_2; $T = 2.81$, $p = .045$) (Table 15).

Patients versus Controls: Fixed Changing to Sway-referenced Floor – Stationary Surround

When participants viewed a stationary visual stimulus while standing on a platform that changed from fixed to sway-referenced, there was increased HbO_2 in the right posterior temporal region in the patients in comparison to the healthy controls ($T = 3.51$, $p = .006$, FDR-corrected) (Table 16). Estimated spatial maps (t-test) of the oxyhemoglobin data for the change in cerebral

activation during the five testing conditions using all source-detector combinations for the six regions of interest are shown in Figures 12 through 16.

Table 12. Change in cerebral activation when viewing single sine optic flow and standing on a fixed surface in patients with complaints of visual vertigo compared to healthy controls. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Region of Interest	Chromophore	Beta	Standard Error	T	*p*	*q*
Left anterior temporal	HbO_2	-2.53	0.64	-3.95	< 0.001	0.002*
	Hb	-0.19	0.45	-0.44	0.66	0.88
Left posterior temporal	HbO_2	0.89	1.06	0.84	0.40	0.69
	Hb	1.10	0.76	1.44	0.15	0.43
Right anterior temporal	HbO_2	-3.45	0.75	-4.59	< 0.001	< 0.001*
	Hb	1.07	0.62	1.73	0.08	0.30
Right posterior temporal	HbO_2	-0.46	0.98	-0.46	0.64	0.88
	Hb	0.73	0.86	0.85	0.39	0.69
Left occipital	HbO_2	0.14	0.78	0.17	0.86	0.96
	Hb	-0.27	0.59	-0.45	0.65	0.88
Right occipital	HbO_2	-0.98	0.86	-1.15	0.25	0.51
	Hb	0.71	0.64	1.12	0.27	0.51

Figure 12. Estimated spatial maps (T-test) of the oxyhemoglobin data collected using fNIRS for the change in cerebral activation between patients and healthy controls when viewing single sine optic flow and standing on a fixed surface using all source-detector combinations. The color bar represents the results of the T-statistic (T-score). Areas in red indicate greater cerebral activation (increased oxyhemoglobin) and areas in blue indicate lesser cerebral activation (decreased oxyhemoglobin) during the comparison. Thick lines indicate areas with significant activation ($p < 0.05$).

Table 13. Change in cerebral activation when viewing sum of sines optic flow and standing on a fixed surface in patients with complaints of visual vertigo compared to healthy controls. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; p = p-value; q = q-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Region of Interest	Chromophore	Beta	Standard Error	T	*p*	*q*
Left anterior temporal	HbO_2	-2.51	0.68	-3.71	< 0.001	< 0.01*
	Hb	-0.94	0.46	-2.05	0.04	0.20
Left posterior temporal	HbO_2	1.75	1.15	1.53	0.13	0.41
	Hb	-0.92	0.79	-1.16	0.25	0.51
Right anterior temporal	HbO_2	-2.34	0.74	-3.16	< 0.01	0.02*
	Hb	-0.08	0.62	-0.13	0.90	0.96
Right posterior temporal	HbO_2	0.14	1.02	0.14	0.89	0.96
	Hb	0.43	0.85	0.50	0.62	0.88
Left occipital	HbO_2	-0.18	0.78	-0.24	0.81	0.96
	Hb	0.80	0.59	1.36	0.17	0.46
Right occipital	HbO_2	-0.43	0.82	-0.53	0.60	0.88
	Hb	0.73	0.63	1.15	0.25	0.51

Figure 13. Estimated spatial maps (T-test) of the oxyhemoglobin data collected using fNIRS for the change in cerebral activation between patients and healthy controls when viewing sum of sines optic flow and standing on a fixed surface using all source-detector combinations. The color bar represents the results of the T-statistic (T-score). Areas in red indicate greater cerebral activation (increased oxyhemoglobin) and areas in blue indicate lesser cerebral activation (decreased oxyhemoglobin) during the comparison. Thick lines indicate areas with significant activation ($p < 0.05$).

Table 14. Change in cerebral activation when viewing single sine optic flow and standing on a sway-referenced surface in patients with complaints of visual vertigo compared to healthy controls. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Region of Interest	Chromophore	Beta	Standard Error	T	*p*	*q*
Left anterior temporal	HbO_2	0.32	0.65	0.49	0.63	0.88
	Hb	-1.23	0.45	-2.73	0.01	0.05
Left posterior temporal	HbO_2	1.64	1.10	1.49	0.14	0.41
	Hb	-1.41	0.78	-1.80	0.07	0.29
Right anterior temporal	HbO_2	-1.40	0.76	-1.83	0.07	0.29
	Hb	-1.52	0.62	-2.46	0.01	0.09
Right posterior temporal	HbO_2	0.35	1.00	0.35	0.72	0.90
	Hb	-2.15	0.84	-2.57	0.01	0.07
Left occipital	HbO_2	-0.31	0.80	-0.39	0.70	0.90
	Hb	0.11	0.60	0.18	0.86	0.96
Right occipital	HbO_2	-0.32	0.87	-0.37	0.71	0.90
	Hb	0.05	0.63	0.09	0.93	0.97

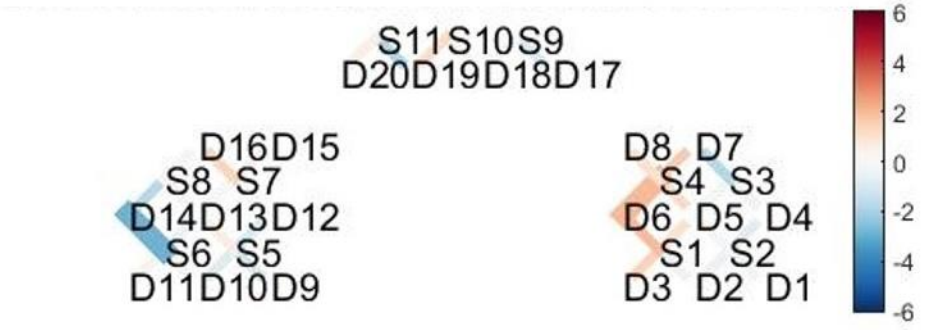


Figure 14. Estimated spatial maps (T-test) of the oxyhemoglobin data collected using fNIRS for the change in cerebral activation between patients and healthy controls when viewing single sine optic flow and standing on a sway-referenced surface using all source-detector combinations. The color bar represents the results of the T-statistic (T-score). Areas in red indicate greater cerebral activation (increased oxyhemoglobin) and areas in blue indicate lesser cerebral activation (decreased oxyhemoglobin) during the comparison. Thick lines indicate areas with significant activation ($p < 0.05$).

Table 15. Change in cerebral activation when viewing sum of sines optic flow and standing on a sway-referenced surface in patients with complaints of visual vertigo compared to healthy controls. Degrees of freedom = 8,352. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; p = p-value; q = q-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Region of Interest	Chromophore	Beta	Standard Error	T	*p*	*q*
Left anterior temporal	HbO_2	-1.32	0.63	-2.09	0.04	0.20
	Hb	0.29	0.45	0.65	0.52	0.82
Left posterior temporal	HbO_2	0.88	1.03	0.86	0.39	0.69
	Hb	0.03	0.80	0.04	0.97	0.97
Right anterior temporal	HbO_2	-3.11	0.76	-4.10	< 0.001	< 0.01*
	Hb	1.72	0.61	2.81	0.01	0.05*
Right posterior temporal	HbO_2	-2.04	1.01	-2.02	0.04	0.20
	Hb	0.69	0.85	0.81	0.42	0.70
Left occipital	HbO_2	-1.05	0.77	-1.36	0.17	0.46
	Hb	0.31	0.62	0.50	0.61	0.88
Right occipital	HbO_2	0.23	0.84	0.28	0.78	0.96
	Hb	-0.09	0.64	-0.13	0.89	0.96

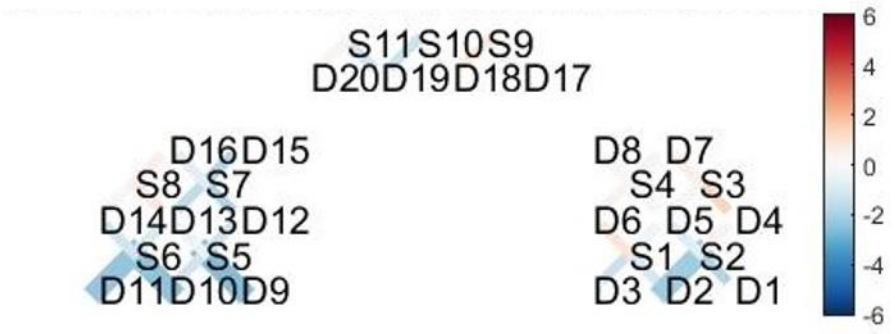


Figure 15. Estimated spatial maps (T-test) of the oxyhemoglobin data collected using fNIRS for the change in cerebral activation between patients and healthy controls when viewing sum of sines optic flow and standing on a sway-referenced surface using all source-detector combinations. The color bar represents the results of the T-statistic (T-score). Areas in red indicate greater cerebral activation (increased oxyhemoglobin) and areas in blue indicate lesser cerebral activation (decreased oxyhemoglobin) during the comparison. Thick lines indicate areas with significant activation ($p < 0.05$).

Table 16. Change in cerebral activation when viewing a stationary visual stimulus and standing on a platform changing from fixed to sway-referenced in patients with complaints of visual vertigo compared to healthy controls. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; p = p-value; q = q-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Region of Interest	Chromophore	Beta	Standard Error	T	*p*	*q*
Left anterior temporal	HbO_2	0.15	0.65	0.23	0.82	0.96
	Hb	-0.57	0.47	-1.24	0.22	0.51
Left posterior temporal	HbO_2	-1.11	1.03	-1.08	0.28	0.53
	Hb	0.91	0.80	1.13	0.26	0.51
Right anterior temporal	HbO_2	-1.07	0.71	-1.49	0.14	0.41
	Hb	-0.66	0.59	-1.13	0.26	0.51
Right posterior temporal	HbO_2	3.53	1.01	3.51	< 0.01	0.01*
	Hb	-1.60	0.90	-1.78	0.08	0.29
Left occipital	HbO_2	0.05	0.84	0.05	0.96	0.97
	Hb	-0.69	0.62	-1.12	0.26	0.51
Right occipital	HbO_2	0.03	0.83	0.04	0.97	0.97
	Hb	-0.50	0.64	-0.77	0.44	0.71

Figure 16. Estimated spatial maps (T-test) of the oxyhemoglobin data collected using fNIRS for the change in cerebral activation between patients and healthy controls when viewing a stationary visual stimulus and standing on a platform changing from fixed to sway-referenced using all source-detector combinations. The color bar represents the results of the T-statistic (T-score). Areas in red indicate greater cerebral activation (increased oxyhemoglobin) and areas in blue indicate lesser cerebral activation (decreased oxyhemoglobin) during the comparison. Thick lines indicate areas with significant activation ($p < 0.05$).

Single Sine versus Sum of Sines Optic Flow

Single sine optic flow resulted in significant increases in HbO_2 and decreases in Hb in all regions of interest except for the occipital region in comparison to a stationary visual field (Table 17). In the occipital region of interest, only the left side showed increased HbO_2 in comparison to a stationary visual field ($T = 5.09$, $p < .0001$, FDR-corrected). Sum of sines optic flow resulted in significant increases in HbO_2 and decreased in Hb in all regions of interest except for Hb in the occipital regions in comparison to a stationary visual field (see Table 16). There was less cerebral activation during sum of sines than single sine optic flow, $F_{(2,1406)} = 86.614$, $p < .0001$ (Figure 17).

Table 17. Change in cerebral activation when viewing single sine or sum of sines optic flow. Beta = regression coefficients; HbO_2 = oxyhemoglobin; Hb = deoxyhemoglobin; *p* = *p*-value; *q* = *q*-value; T = T-statistic; * indicates $p \leq 0.05$, false discovery rate-corrected.

Optic Flow Condition	Region of Interest	Chromo-phore	Beta	Standard Error	T	*p*	*q*
Single Sine	Left anterior temporal	HbO_2	5.29	0.51	10.23	< 0.001	< 0.001*
		Hb	-1.11	0.26	-4.21	< 0.001	< 0.001*
	Left posterior temporal	HbO_2	5.52	0.94	5.85	< 0.001	< 0.001*
		Hb	-5.42	0.62	-8.74	< 0.001	< 0.001*
	Right anterior temporal	HbO_2	4.29	0.74	5.83	< 0.001	< 0.001*
		Hb	-3.76	0.51	-7.36	< 0.001	< 0.001*
	Right posterior temporal	HbO_2	8.21	0.94	8.77	< 0.001	< 0.001*
		Hb	-6.34	0.65	-9.74	< 0.001	< 0.001*
	Left occipital	HbO_2	6.41	1.26	5.09	< 0.001	< 0.001*
		Hb	-0.47	0.47	-1.01	0.31	0.34
	Right occipital	HbO_2	2.66	1.19	2.24	0.03	0.03
		Hb	0.002	0.35	0.005	1.00	1.00
Sum of Sines	Left anterior temporal	HbO_2	4.61	0.56	8.20	< 0.001	< 0.001*
		Hb	-3.16	0.29	-10.89	< 0.001	< 0.001*
	Left posterior temporal	HbO_2	8.21	1.02	8.08	< 0.001	< 0.001*
		Hb	-8.17	0.72	-11.34	< 0.001	< 0.001*
	Right anterior temporal	HbO_2	5.66	0.70	8.07	< 0.001	< 0.001*
		Hb	-4.41	0.49	-8.94	< 0.001	< 0.001*
	Right posterior temporal	HbO_2	9.38	1.08	8.69	< 0.001	< 0.001*
		Hb	-6.11	0.67	-9.16	< 0.001	< 0.001*
	Left occipital	HbO_2	5.12	1.22	4.18	< 0.001	< 0.001*
		Hb	-0.05	0.51	-0.09	0.93	0.97
	Right occipital	HbO_2	7.13	1.29	5.52	< 0.001	< 0.001*
		Hb	0.61	0.43	1.42	0.16	0.18

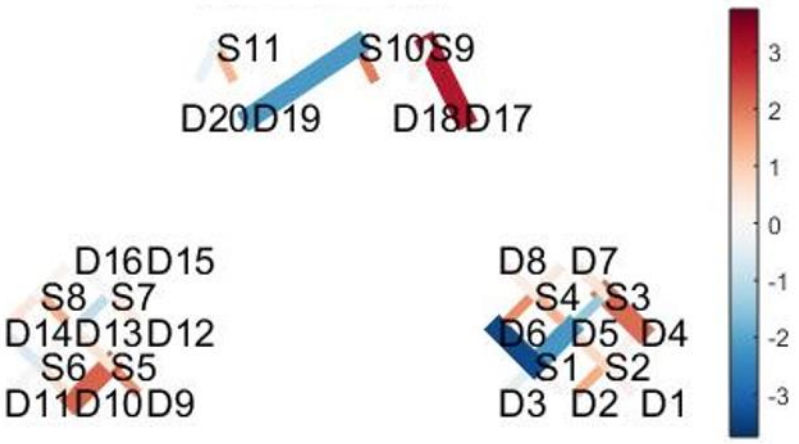


Figure 17. Estimated spatial maps (T-test) of the oxyhemoglobin data collected using fNIRS for the change in cerebral activation between sum of sines and single sine optic flow using all source-detector combinations. The color bar represents the results of the T-statistic (T-score). Areas in red indicate greater cerebral activation (increased oxyhemoglobin) and areas in blue indicate lesser cerebral activation (decreased oxyhemoglobin) during the comparison. Thick lines indicate areas with significant activation ($p < 0.05$).

4.3.1.2 Postural sway with optic flow

Statistical analyses using a linear mixed-effects model revealed significantly more sway in both the patients and the healthy controls in response to the moving visual and platform conditions. The models fit the data well, as determined by the values of the AIC and BIC (Table 18). The changes observed in the patients and the healthy controls are described below for the twelve dependent variables.

Table 18. Information Criterion values for the models with compound symmetry heterogeneous covariance structure. AIC = Akaike's Information Criterion; AP = anterior-posterior; BIC = Schwartz's Bayesian Information Criterion; CSH = compound symmetry heterogeneous; ML = medial-lateral; NPL = normalized path length; RMS = root mean square.

Dependent Variable	AIC	BIC
Head AP NPL	397.24	431.13
Head AP RMS	407.57	441.46
Head ML NPL	-384.38	-350.49
Head ML RMS	-299.71	-265.82
Hips AP NPL	249.63	283.52
Hips AP RMS	218.65	252.54
Hips ML NPL	-434.83	-400.94
Hips ML RMS	-376.04	-342.14
COP AP NPL	433.51	467.40
COP AP RMS	252.19	286.08
COP ML NPL	-174.42	-140.53
COP ML RMS	-299.34	-265.45

Head Anterior-Posterior Normalized Path Length

There were significant main effects for group ($F_{(1,36)} = 5.05$, $p = .031$), condition ($F_{(3,45)} = 34.95$, $p < .001$), and period ($F_{(1,64)} = 109.35$, $p < .001$). There were significant group by period ($F_{(1,36)} = 7.13$, $p = .011$) and condition by period ($F_{(3,85)} = 11.99$, $p < .001$) interaction effects for anterior-posterior NPL movement of the head. Both the patients with visual vertigo and the healthy controls had greater anterior-posterior NPL movement of the head during optic flow periods than stationary surround periods (Table 19). The mean difference in anterior-posterior NPL movement of the head during optic flow periods and stationary surround periods was larger in the patients with visual vertigo. Across all four conditions, anterior-posterior NPL movement of the head was always greater during optic flow periods than stationary surround periods (Table 20).

Table 19. Average anterior-posterior normalized path length movement of the head during the two periods for the patients and healthy controls.

Group	Period	Mean	Standard Error
Patients	Stationary Surround	1.32	0.16
	Optic Flow	2.55	0.24
Healthy Controls	Stationary Surround	0.95	0.15
	Optic Flow	1.76	0.23

Table 20. Average anterior-posterior normalized path length movement of the head during the four conditions for the two periods.

Condition	Period	Mean	Standard Error
Fixed Floor –Single Sine	Stationary Surround	0.59	0.05
	Optic Flow	1.22	0.15
Fixed Floor – Sum of Sines	Stationary Surround	0.59	0.05
	Optic Flow	1.07	0.11
Sway-referenced Floor – Single Sine	Stationary Surround	1.67	0.24
	Optic Flow	3.34	0.30
Sway-referenced Floor – Sum of Sines	Stationary Surround	1.70	0.21
	Optic Flow	2.97	0.24

Head Anterior-Posterior Root Mean Square

There were significant main effects for condition ($F_{(3,48)} = 39.80$, $p < .001$) and period ($F_{(1,89)} = 62.52$, $p < .001$). There were significant group by period ($F_{(1,44)} = 5.27$, $p = .027$) and condition by period ($F_{(3,70)} = 3.94$, $p = .012$) interaction effects for anterior-posterior RMS movement of the head. Both the patients with visual vertigo and the healthy controls had greater anterior-posterior RMS movement of the head during optic flow periods than stationary surround periods (Table 21). Across all four conditions, anterior-posterior RMS movement of the head was always greater during optic flow periods than stationary surround periods (Table 22).

Table 21. Average anterior-posterior root mean square movement of the head during the two periods for the patients and healthy controls.

Group	Period	Mean	Standard Error
Patients	Stationary Surround	1.50	0.22
	Optic Flow	2.15	0.25
Healthy Controls	Stationary Surround	1.12	0.21
	Optic Flow	1.54	0.24

Table 22. Average anterior-posterior root mean square movement of the head during the four conditions for the two periods.

Condition	Period	Mean	Standard Error
Fixed Floor –Single Sine	Stationary Surround	0.63	0.11
	Optic Flow	1.01	0.15
Fixed Floor – Sum of Sines	Stationary Surround	0.69	0.11
	Optic Flow	0.95	0.13
Sway-referenced Floor – Single Sine	Stationary Surround	1.95	0.26
	Optic Flow	2.73	0.24
Sway-referenced Floor – Sum of Sines	Stationary Surround	1.98	0.25
	Optic Flow	2.68	0.24

Head Medial-Lateral Normalized Path Length

There were significant main effects for condition ($F_{(3,45)} = 29.06$, $p < .001$) and period ($F_{(1,76)} = 61.95$, $p < .001$). There was a significant condition by period ($F_{(3,76)} = 9.60$, $p < .001$) interaction effect for medial-lateral NPL movement of the head. Across all four conditions, medial-lateral NPL movement of the head was always greater during optic flow periods than stationary surround periods (Table 23).

Table 23. Average medial-lateral normalized path length movement of the head during the four conditions for the two periods.

Condition	Period	Mean	Standard Error
Fixed Floor –Single Sine	Stationary Surround	0.39	0.04
	Optic Flow	0.42	0.04
Fixed Floor – Sum of Sines	Stationary Surround	0.38	0.03
	Optic Flow	0.41	0.03
Sway-referenced Floor – Single Sine	Stationary Surround	0.52	0.05
	Optic Flow	0.65	0.05
Sway-referenced Floor – Sum of Sines	Stationary Surround	0.50	0.04
	Optic Flow	0.63	0.05

Head Medial-Lateral Root Mean Square

There were significant main effects for condition ($F_{(3,45)}$ = 25.32, p < .001) and period ($F_{(1,124)}$ = 8.78, p = .004) for medial-lateral RMS movement of the head. There was no main effect for group ($F_{(1,28)}$ = 0.06, p = .810). The average medial-lateral RMS movement of the head is presented in Table 24. Pairwise comparisons revealed that the fixed floor conditions were not different from each other (p = .999) and that the sway-referenced floor conditions were not different from each other (p = .930). The fixed conditions were different from the sway-referenced conditions, all p < .001. There was greater medial-lateral RMS movement of the head during optic flow periods (M 0.40, SE 0.03) than stationary surround periods (M 0.37, SE 0.03), p = .004.

Table 24. Average medial-lateral root mean square movement of the head during the four conditions.

Condition	Mean	Standard Error
Fixed Floor –Single Sine	0.33	0.03
Fixed Floor – Sum of Sines	0.32	0.03
Sway-referenced Floor – Single Sine	0.46	0.04
Sway-referenced Floor – Sum of Sines	0.44	0.03

Hips Anterior-Posterior Normalized Path Length

There were significant main effects for group ($F_{(1,34)} = 5.048$, $p = .031$), condition ($F_{(3,48)} = 47.49$, $p < .001$), and period ($F_{(1,90)} = 82.20$, $p < .001$). There were significant group by period ($F_{(1,45)} = 4.88$, $p = .032$) and condition by period ($F_{(3,82)} = 6.35$, $p = .001$) interaction effects for anterior-posterior NPL movement of the hips. Both the patients with visual vertigo and the healthy controls had greater anterior-posterior NPL movement of the hips during optic flow periods than stationary surround periods (Table 25). The mean difference in anterior-posterior NPL movement of the hips during optic flow periods and stationary surround periods was larger in the patients with visual vertigo. Across all four conditions, anterior-posterior NPL movement of the hips was always greater during optic flow periods than stationary surround periods (Table 26).

Table 25. Average anterior-posterior normalized path length movement of the hips during the two periods for the patients and healthy controls.

Group	Period	Mean	Standard Error
Patients	Stationary Surround	0.92	0.10
	Optic Flow	1.66	0.15
Healthy Controls	Stationary Surround	0.68	0.10
	Optic Flow	1.16	0.15

Table 26. Average medial-lateral normalized path length movement of the head during the four conditions for the two periods.

Condition	Period	Mean	Standard Error
Fixed Floor –Single Sine	Stationary Surround	0.32	0.02
	Optic Flow	0.71	0.10
Fixed Floor – Sum of Sines	Stationary Surround	0.33	0.03
	Optic Flow	0.65	0.08
Sway-referenced Floor – Single Sine	Stationary Surround	1.25	0.16
	Optic Flow	2.24	0.18
Sway-referenced Floor – Sum of Sines	Stationary Surround	1.29	0.16
	Optic Flow	2.03	0.16

Hips Anterior-Posterior Root Mean Square

There were significant main effects for condition ($F_{(3,49)}$ = 50.51, p < .001) and period ($F_{(1,115)}$ = 25.40, p < .001) for anterior-posterior RMS movement of the hips. There was no main effect for group ($F_{(1,35)}$ = 1.89, p = .177). The average anterior-posterior RMS movement of the hips is presented in Table 27. Pairwise comparisons revealed that the fixed floor conditions were not different from each other (p = 1.000) and that the sway-referenced floor conditions were not different from each other (p = 1.000). The fixed conditions were different from the sway-referenced conditions, all p < .001. There was greater anterior-posterior RMS movement of the hips during optic flow periods (M 1.22, SE 0.10) than stationary surround periods (M 0.96, SE 0.09), p < .001.

Table 27. Average anterior-posterior root mean square movement of the hips during the four conditions.

Condition	Mean	Standard Error
Fixed Floor –Single Sine	0.49	0.05
Fixed Floor – Sum of Sines	0.48	0.05
Sway-referenced Floor – Single Sine	1.69	0.15
Sway-referenced Floor – Sum of Sines	1.69	0.14

Hips Medial-Lateral Normalized Path Length

There were significant main effects for condition ($F_{(3,42)}$ = 36.95, p < .001) and period ($F_{(1,69)}$ = 53.68, p < .001). There was a significant condition by period ($F_{(3,70)}$ = 6.17, p = .001) interaction effect for medial-lateral NPL movement of the hips. Across all four conditions, medial-lateral NPL movement of the hips was always greater during optic flow periods than stationary surround periods (Table 28).

Table 28. Average medial-lateral normalized path length movement of the hips during the four conditions for the two periods.

Condition	Period	Mean	Standard Error
Fixed Floor –Single Sine	Stationary Surround	0.17	0.02
	Optic Flow	0.21	0.02
Fixed Floor – Sum of Sines	Stationary Surround	0.17	0.02
	Optic Flow	0.20	0.02
Sway-referenced Floor – Single Sine	Stationary Surround	0.30	0.03
	Optic Flow	0.41	0.04
Sway-referenced Floor – Sum of Sines	Stationary Surround	0.29	0.03
	Optic Flow	0.40	0.04

Hips Medial-Lateral Root Mean Square

There were significant main effects for condition ($F_{(3,122)} = 41.29$, $p < .001$) and period ($F_{(1,116)} = 8.50$, $p = .004$) for medial-lateral RMS movement of the hips. There was no main effect for group ($F_{(1,35)} = 0.06$, $p = .805$). The average medial-lateral RMS movement of the hips is presented in Table 29. Pairwise comparisons revealed that the fixed floor conditions were not different from each other ($p = 1.000$) and that the sway-referenced floor conditions were not different from each other ($p = 0.249$). The fixed conditions were different from the sway-referenced conditions, all $p < .001$. There was greater medial-lateral RMS movement of the hips during optic flow periods (M 0.29, SE 0.03) than stationary surround periods (M 0.26, SE 0.02), $p = .004$.

Table 29. Average medial-lateral root mean square movement of the hips during the four conditions.

Condition	Mean	Standard Error
Fixed Floor –Single Sine	0.23	0.03
Fixed Floor – Sum of Sines	0.22	0.03
Sway-referenced Floor – Single Sine	0.35	0.03
Sway-referenced Floor – Sum of Sines	0.32	0.02

Center of Pressure Anterior-Posterior Normalized Path Length

There were significant main effects for condition ($F_{(3,46)}$ = 64.40, p < .001) and period ($F_{(1,47)}$ = 103.04, p < .001). There was a significant condition by period ($F_{(3,83)}$ = 13.39, p < .001) interaction effect for anterior-posterior NPL movement of the COP. Across all four conditions, anterior-posterior NPL movement of the COP was always greater during optic flow periods than stationary surround periods (Table 30).

Table 30. Average anterior-posterior normalized path length movement of the center of pressure during the four conditions for the two periods.

Condition	Period	Mean	Standard Error
Fixed Floor –Single Sine	Stationary Surround	0.56	0.04
	Optic Flow	1.32	0.17
Fixed Floor – Sum of Sines	Stationary Surround	0.60	0.05
	Optic Flow	1.25	0.14
Sway-referenced Floor – Single Sine	Stationary Surround	2.07	0.20
	Optic Flow	4.05	0.32
Sway-referenced Floor – Sum of Sines	Stationary Surround	2.11	0.19
	Optic Flow	3.75	0.28

Center of Pressure Anterior-Posterior Root Mean Square

There were significant main effects for condition ($F_{(3,48)}$ = 48.08, p < .001) and period ($F_{(1,116)}$ = 45.72, p < .001). There was a significant group by period ($F_{(1,48)}$ = 4.74, p = .034) interaction effect for the anterior-posterior RMS movement of the COP. Both the patients with visual vertigo and the healthy controls had greater anterior-posterior RMS movement of the COP during optic flow periods than stationary surround periods (Table 31). The mean difference in anterior-posterior RMS movement of the COP during optic flow periods and stationary surround periods was larger in the patients with visual vertigo.

Table 31. Average anterior-posterior root mean square movement of the center of pressure during the two periods for the patients and healthy controls.

Group	Period	Mean	Standard Error
Patients	Stationary Surround	1.09	0.12
	Optic Flow	1.61	0.15
Healthy Controls	Stationary Surround	0.86	0.12
	Optic Flow	1.16	0.15

Center of Pressure Medial-Lateral Normalized Path Length

There were significant main effects for condition ($F_{(3,46)} = 36.01$, $p < .001$) and period ($F_{(1,42)} = 47.27$, $p < .001$). There was a significant condition by period ($F_{(3,53)} = 9.39$, $p < .001$) interaction effect for medial-lateral NPL movement of the COP. Across all four conditions, medial-lateral NPL movement of the COP was always greater during optic flow periods than stationary surround periods (Table 32).

Table 32. Average medial-lateral normalized path length movement of the center of pressure during the four conditions for the two periods.

Condition	Period	Mean	Standard Error
Fixed Floor –Single Sine	Stationary Surround	0.26	0.02
	Optic Flow	0.34	0.04
Fixed Floor – Sum of Sines	Stationary Surround	0.27	0.03
	Optic Flow	0.33	0.03
Sway-referenced Floor – Single Sine	Stationary Surround	0.53	0.05
	Optic Flow	0.86	0.08
Sway-referenced Floor – Sum of Sines	Stationary Surround	0.55	0.05
	Optic Flow	0.84	0.08

Center of Pressure Medial-Lateral Root Mean Square

There were significant main effects for condition ($F_{(3,49)} = 9.37$, $p < .001$) and period ($F_{(1,45)} = 16.83$, $p < .001$). There was a significant condition by period ($F_{(3,65)} = 3.02$, $p = .036$) interaction effect for medial-lateral RMS movement of the COP. Across all four conditions,

medial-lateral RMS movement of the COP was always greater during optic flow periods than stationary surround periods (Table 33).

Table 33. Average medial-lateral root mean square movement of the center of pressure during the four conditions for the two periods.

Condition	Period	Mean	Standard Error
Fixed Floor –Single Sine	Stationary Surround	0.20	0.04
	Optic Flow	0.22	0.04
Fixed Floor – Sum of Sines	Stationary Surround	0.20	0.04
	Optic Flow	0.22	0.04
Sway-referenced Floor – Single Sine	Stationary Surround	0.34	0.06
	Optic Flow	0.45	0.08
Sway-referenced Floor – Sum of Sines	Stationary Surround	0.35	0.07
	Optic Flow	0.43	0.08

4.3.1.3 Postural sway with a stationary surround

Statistical analyses using a linear mixed-effects model revealed significantly more sway in both the patients and the healthy controls during the sway-referenced floor period during the condition when the floor changed from fixed to sway-referenced and the visual surround was stationary. The models fit the data well, as determined by the values of the AIC and BIC (Table 34). The changes observed in the patients and the healthy controls are described below for the twelve dependent variables.

Table 34. Information Criterion values for the models with Toeplitz covariance structure. AIC = Akaike's Information Criterion; AP = anterior-posterior; BIC = Schwartz's Bayesian Information Criterion; CSH = compound symmetry heterogeneous; ML = medial-lateral; NPL = normalized path length; RMS = root mean square.

Dependent Variable	AIC	BIC
Head AP NPL	148.65	154.61
Head AP RMS	153.59	159.56
Head ML NPL	-19.26	-13.29
Head ML RMS	-24.78	-18.81
Hips AP NPL	132.95	138.92
Hips AP RMS	121.77	127.73
Hips ML NPL	-44.02	-38.06
Hips ML RMS	-45.72	-39.75
COP AP NPL	158.81	164.77
COP AP RMS	133.69	139.66
COP ML NPL	2.33	8.29
COP ML RMS	-11.65	-5.69

Head Anterior-Posterior Normalized Path Length

There was a significant main effect for period ($F_{(1,27)}$ = 31.32, p < .001). There was no main effect for group ($F_{(1,27)}$ = 1.20, p = .283). There was greater anterior-posterior NPL movement of the head during sway-referenced floor periods (M 1.74, SE 0.15) than fixed floor periods (M 0.64, SE 0.15), p < .001.

Head Anterior-Posterior Root Mean Square

There was a significant main effect for period ($F_{(1,27)}$ = 56.91, p < .001). There was no main effect for group ($F_{(1,27)}$ = 0.97, p = .333). There was greater anterior-posterior RMS movement of the head during sway-referenced floor periods (M 2.02, SE 0.17) than fixed floor periods (M 0.71, SE 0.17), p < .001.

Head Medial-Lateral Normalized Path Length

There was a significant main effect for period ($F_{(1,27)}$ = 26.37, p < .001). There was no main effect for group ($F_{(1,27)}$ = 0.66, p = .425). There was greater medial-lateral NPL movement

of the head during sway-referenced floor periods (M 0.54, SE 0.04) than fixed floor periods (M 0.37, SE 0.04), $p < .001$.

Head Medial-Lateral Root Mean Square

There was a significant main effect for period ($F_{(1,27)} = 25.09$, $p < .001$). There was no main effect for group ($F_{(1,27)} = 0.02$, $p = .890$). There was greater medial-lateral RMS movement of the head during sway-referenced floor periods (M 0.46, SE 0.04) than fixed floor periods (M 0.32, SE 0.04), $p < .001$.

Hips Anterior-Posterior Normalized Path Length

There was a significant main effect for period ($F_{(1,27)} = 34.79$, $p < .001$). There was no main effect for group ($F_{(1,27)} = 1.46$, $p = .238$). There was greater anterior-posterior NPL movement of the hips during sway-referenced floor periods (M 1.42, SE 0.13) than fixed floor periods (M 0.37, SE 0.13), $p < .001$.

Hips Anterior-Posterior Root Mean Square

There was a significant main effect for period ($F_{(1,27)} = 60.32$, $p < .001$). There was no main effect for group ($F_{(1,27)} = 0.20$, $p = .656$). There was greater anterior-posterior RMS movement of the hips during sway-referenced floor periods (M 1.60, SE 0.12) than fixed floor periods (M 0.38, SE 0.12), $p < .001$.

Hips Medial-Lateral Normalized Path Length

There was a significant main effect for period ($F_{(1,27)} = 30.88$, $p < .001$). There was no main effect for group ($F_{(1,27)} = 0.01$, $p = .920$). There was greater medial-lateral NPL movement of the hips during sway-referenced floor periods (M 0.33, SE 0.03) than fixed floor periods (M 0.17, SE 0.03), $p < .001$.

Hips Medial-Lateral Root Mean Square

There was a significant main effect for period ($F_{(1,27)}$ = 36.24, p < .001). There was no main effect for group ($F_{(1,27)}$ = 0.14, p = .709). There was greater medial-lateral RMS movement of the hips during sway-referenced floor periods (M 0.36, SE 0.03) than fixed floor periods (M 0.22, SE 0.03), p < .001.

Center of Pressure Anterior-Posterior Normalized Path Length

There was a significant main effect for period ($F_{(1,27)}$ = 36.30, p < .001). There was no main effect for group ($F_{(1,27)}$ = 1.41, p = .245). There was greater anterior-posterior NPL movement of the COP during sway-referenced floor periods (M 2.09, SE 0.17) than fixed floor periods (M 0.68, SE 0.17), p < .001.

Center of Pressure Anterior-Posterior Root Mean Square

There was a significant main effect for period ($F_{(1,27)}$ = 51.35, p < .001). There was no main effect for group ($F_{(1,27)}$ = 0.46, p = .502). There was greater anterior-posterior RMS movement of the COP during sway-referenced floor periods (M 1.65, SE 0.13) than fixed floor periods (M 0.39, SE 0.13), p < .001.

Center of Pressure Medial-Lateral Normalized Path Length

There was a significant main effect for period ($F_{(1,27)}$ = 47.73, p < .001). There was no main effect for group ($F_{(1,27)}$ = 0.003, p = .954). There was greater medial-lateral NPL movement of the COP during sway-referenced floor periods (M 0.57, SE 0.04) than fixed floor periods (M 0.26, SE 0.04), p < .001.

Center of Pressure Medial-Lateral Root Mean Square

There was a significant main effect for period ($F_{(1,27)}$ = 20.26, p < .001). There was no main effect for group ($F_{(1,27)}$ = 0.09, p = .767). There was greater medial-lateral RMS movement

of the COP during sway-referenced floor periods (M 0.38, SE 0.04) than fixed floor periods (M 0.21, SE 0.04), $p < .001$.

4.4 DISCUSSION

In this study, fNIRS was used to investigate cortical activity in patients with visual vertigo and healthy controls during single sine and sum of sines optic flow while standing on a fixed or sway-referenced surface. The primary finding was decreased activation in the bilateral anterior temporal regions in the patient group when viewing optic flow while standing on a fixed surface in comparison to the healthy controls. Decreased activation was also seen in the right anterior temporal region in the patient group when viewing sum of sines optic flow while standing on a sway-referenced surface in comparison to the healthy controls. Patients with visual vertigo show less cerebral activation in regions associated with multi-sensory integration in comparison to healthy controls. This decreased activation may represent an altered ability to perform sensory re-weighting of visual and vestibular information, leading to symptoms of dizziness and imbalance.

Patients were well matched with their healthy controls. Age, height, weight, and education were not different between groups. The participants were matched for gender. Given the relatively high proportion of patients with a diagnosis of vestibular migraine in this study, it is not surprising that the sample was comprised of 67% women. Vestibular migraine predominantly affects women by a ratio of about 5:1.(Neuhauser, Leopold, Von Brevern, Arnold, & Lempert, 2001) Additionally, PPPD was more common in female patients in an observational study in China.(Yan et al., 2017) Only right-handed participants were included, as

hemispheric functional specialization is known to be more diffuse in left-handed individuals.(Hatta, 2007)

The patients reported a mean score of 58 for both the modified VVAS and the six exploratory items. In an earlier sample of 92 patients reporting to the same clinical practice that patients for this study were recruited from, a seventy-fifth percentile of 53.0, mean of 32.9, and standard deviation of 26.0 were recorded. This is consistent with the seventy-fifth percentile of 51.9, mean of 30.3, and standard deviation of 26.7 reported in the vestibular group described by Dannenbaum et al.(Dannenbaum et al., 2011) The mean visual vertigo severity score for patients included in this study was above these seventy-fifth percentiles, and supports the diagnosis of visual vertigo in the patient group. There is a positive correlation (r = 0.54) between the VVAS and the DHI.(Grigol et al., 2015) It was not surprising that the patients were moderately to severely handicapped by their dizziness.(Whitney et al., 2004) Patients with visual vertigo are known to have higher DHI scores than those with vestibular dysfunction without visual vertigo and healthy controls.(Zur et al., 2015)

Greater anxiety and depression was noted in the patients in comparison to the healthy controls. This is similar to the findings of a previously published study comparing patients with vestibular dysfunction and visual vertigo to healthy controls.(Pavlou, Davies, & Bronstein, 2006) Patients with vestibular disorders(Grunfeld, Gresty, Bronstein, & Jahanshahi, 2003) and Meniere's disease(Kirby & Yardley, 2008) are known to have increased anxiety and depression. Abnormal Hospital Anxiety and Depression Scale scores have been noted in patients with Meniere's disease, vestibular migraine, and Meniere's disease plus vestibular migraine.(Neff et al., 2012) Depression scores have been correlated with increased reports of symptoms provoked or aggravated by complex visual stimuli.(Pavlou et al., 2006) The worse depression scores in the

patient group are likely due to the vestibular disorder and activity limitation and participation restriction sequelae.(Staab & Ruckenstein, 2003) Patients with vestibular disorders are known to have increased anxiety.(Guerraz et al., 2001; Pavlou et al., 2006) As observed in this study, increased anxiety has been reported in patients with visual vertigo(Zur et al., 2015), chronic subjective dizziness,(Staab, 2012) and PPPD.(Yan et al., 2017)

The primary specific aim of this study was to examine the effect of single sine and sum of sines optic flow on cerebral activation in patients with complaints of visual vertigo and healthy adults. There were two hypotheses related to this specific aim. First, cerebral activation in the bilateral temporal and occipital lobes would be greater in patients with complaints of visual vertigo than in healthy adults. Second, cerebral activation in the bilateral temporal and occipital lobes would be greater during sum of sines than single sine optic flow.

When viewing single sine or sum of sines optic flow while standing on a fixed surface, the patients displayed less activation in the bilateral anterior temporal regions than the healthy controls. The anterior temporal region of interest overlaid the superior temporal gyrus, a region of sensory-motor integration. When viewing single sine optic flow in comparison to a stationary surround while standing on a fixed platform, the patients had decreased activation in the bilateral anterior temporal regions. The healthy controls, in contrast, showed robust activation in the bilateral anterior temporal regions. This is similar to the results of Indovina et al., who found that patients with chronic subjective dizziness showed activation to a lesser extent in the superior temporal gyrus in comparison to healthy controls.(Indovina et al., 2015) The healthy controls responded robustly to sound-evoked vestibular stimuli, while the patients had less cortical activation, particularly in the right posterior insula and superior temporal gyrus.(Indovina et al., 2015)

In an fMRI study of patients with unilateral vestibular neurectomies, a similar pattern of activation to a lesser extent was seen in the patients in comparison to healthy controls.(Deutschländer et al., 2008) Unlike Deutschländer et al., no differences were seen in the occipital lobes between the two groups in this study. Decreased activation of motion-sensitive regions in patients with unilateral vestibular neurectomies may serve as a way to suppress visual motion perception as a means to decrease visual blurring.(Deutschländer et al., 2008) The heterogeneity of vestibular disorders in the patient group in this study may account for the absence of differences between patients and healthy controls. Very few patients in this study had a pure peripheral vestibular hypofunction that would impair the vestibulo-ocular reflex resulting in visual blurring.

Decreased cortical activation in the bilateral anterior temporal regions in the patients may reflect decreased sensory integration in the superior temporal gyri. Most of the patients had some type of central and/or peripheral vestibular disorder resulting in dizziness. In an attempt to limit dizziness due to visual-vestibular conflict or as a result of diminished afferent vestibular input, the decreased cortical activation could indicate decreased weighting of vestibular information and sensory-motor integration in the superior temporal gyrus. Alternatively, the decreased cortical activation in the bilateral anterior temporal regions in the patients could be due to increased cortical-cortical inhibition.

During resting state fMRI, patients with visually induced dizziness had decreased functional connectivity in the right superior temporal gyrus.(Van Ombergen et al., 2017) In this small sample of ten patients, 9 out of 10 of whom had a peripheral vestibular disorder, the decreased functional connectivity was likely indicative of decreased weighting and sensory integration (cortical-level processing) of vestibular information at rest.(Van Ombergen et al.,

2017) The right-sided dominance observed by Van Ombergen et al. is likely due to all participants being right-handed. The patients in the current study, though all meeting the criteria of being right-handed, displayed some variability in their Edinburgh Handedness Inventory-Short Form. Seven of the patients had laterality quotient scores less than 100, in comparison to only one healthy control. This may account for the bilaterally decreased activation observed in the anterior temporal regions. Comparisons between the current study and that of Van Ombergen et al. are limited by the study design (task-based versus resting) and image acquisition methods (quiet stance on a fixed or sway-referenced surface versus supine).

Similar decreases in functional connectivity were seen in patients with chronic subjective dizziness in comparison to healthy controls using fMRI during sound-evoked vestibular stimulation.(Indovina et al., 2015) The results included functional connectivity changes between the left anterior insula/inferior frontal gyrus and the right superior temporal gyrus, and between the left hippocampus and right superior temporal gyrus.(Indovina et al., 2015) The decreased cortical activity and functional connectivity of vestibular processing may lead to dizziness and unsteadiness.(Indovina et al., 2015) As underlying changes in cortical connectivity both at rest and during sound-evoked vestibular stimulation are present in patients with visually induced and chronic subjective dizziness, it is not surprising that task-based functional changes in cortical activation were seen in the patients with complaints of visual vertigo in this study.

The participants in the studies by Indovina et al. and Van Ombergen et al. are similar to the patients in this study. The patient population in this study all reported complaints of visual vertigo as measured on the VVAS. The patients with visually induced dizziness all reported complaints of visual vestibular mismatch using the questionnaire proposed by Mallinson,(Mallinson, 2011) all of the items of which are incorporated into the VVAS. One of

the diagnostic criteria for chronic subjective dizziness is symptoms of dizziness and/or unsteadiness exacerbated by moving or complex visual stimuli.("ICD-11 Beta Draft,") Although the patient groups are similar, comparisons between the current study and these fMRI studies are limited by the study designs (task-based versus resting and visual versus auditory stimuli) and image acquisition methods (quiet stance on a fixed or sway-referenced surface versus supine).

When viewing single sine optic flow while standing on a sway-referenced surface, there were no differences in the pattern of activation between the patients and healthy controls. The patients robustly activated the left anterior and posterior temporal as well as the right posterior temporal regions. The activation of the right anterior temporal region was much less. There was also bilateral activation of the occipital regions, but to a much lesser extent than all other regions of interest except the right anterior temporal region. This reflects decreased activation of the right anterior temporal region of interest, which overlaid the superior temporal gyrus. This is similar to the deactivations seen in the superior and middle temporal gyri in patients with unilateral vestibular neurectomies in response to optokinetic stimuli.(Deutschländer et al., 2008) The healthy controls robustly activated all six regions of interest, to include the right anterior temporal region. An inability to activate the right anterior temporal region may underlie complaints of imbalance in the patient group.

When viewing sum of sines optic flow while standing on a sway-referenced surface, the patients displayed less activation in the right anterior temporal region than the healthy controls. The patients displayed robust activation of the bilateral temporal regions (both anterior and posterior) and lesser activation of the right (more so than the left) occipital region. The healthy controls also displayed robust activation of the bilateral temporal regions and lesser activation of the bilateral occipital regions. This is consistent with the decreased activation of the right

superior temporal region observed in patients with unilateral vestibular neurectomies and chronic subjective dizziness.(Deutschländer et al., 2008; Indovina et al., 2015) An inability to activate the right anterior temporal region may underlie complaints of imbalance in the patient group.

Similar patterns of cerebral activation were observed in response to single sine and sum of sines optic flow while standing on a fixed platform. The patients displayed less cortical activation in the bilateral anterior temporal regions than the healthy controls. The patients displayed less cortical activation in the right anterior temporal region than the healthy controls when viewing sum of sines optic flow and standing on a sway-referenced surface. This pattern was also observed when viewing sum of sines optic flow and standing on a sway-referenced surface, though the decrease was not statistically significant. Given the similarities in cortical activation observed in response to single and sum of sines optic flow, it may be that the type of surface is more important than the type of optic flow for modulating cortical brain responses.

In previous studies using fNIRS, bilateral activation of the superior temporal and supramarginal gryi has been observed during computerized dynamic posturography testing when visual (eyes closed) and proprioceptive (sway-referenced platform) information was degraded.(Karim et al., 2013; Lin, Barker, Sparto, Furman, & Huppert, 2017; Takakura et al., 2015) These brain regions are important for sensory-motor integration and multi-sensory integration, respectively. In this study, visual information was present but was also degraded, in that it was designed to visually perturb standing balance. The healthy controls always displayed bilateral activation of the superior temporal and supramarginal gryi. The inability of the patients to respond in this same manner (failing to activate the right anterior temporal region) may indicate decreased cortical activity used for sensory integration or an altered strategy for the maintenance of balance. This is similar to the decreased activation in the supramarginal gyrus

observed in poorer performing participants during a dance simulation video game.(Ono et al., 2014) These participants were unable to sustain activation of the supramarginal gyrus and had fewer accurate dance steps.(Ono et al., 2014) In the current study, patients were unable to activate the right superior temporal region, resulting in increased postural sway (poorer performance).

The second hypothesis, that cerebral activation in the bilateral temporal and occipital lobes would be greater during sum of sines than single sine optic flow, was disproved. When the effect of surface condition and group was controlled, there was less cerebral activation during sum of sines than single sine optic flow. The greater brain response observed in this study during single sine versus sum of sines optic flow is strikingly similar to the postural response observed a decade ago during single sine versus sum of sines optic flow using an identical visual scene.(Musolino et al., 2006) Optic flow that oscillated linearly in a periodic (or predictable) way induced postural responses that were on average four times larger than optic flow that oscillated in a non-periodic (or unpredictable) way.(Musolino et al., 2006) The sum of sines optic flow was purposely designed to be unpredictable. It, therefore, provides destabilizing visual information and induces decreased weighting of this sensory information. The cortical areas showed less sensory integration (less cortical activation) of this unpredictable or untrustworthy sum of sines optic flow information.

The secondary specific aim of this study was to examine the effect of single sine and sum of sines optic flow on postural sway in patients with complaints of visual vertigo and healthy adults. There were two hypotheses related to this specific aim. First, postural sway would be greater in patients with complaints of visual vertigo than in healthy adults. Second, postural

sway would be greater during sum of sines than single sine optic flow, though both groups would exhibit increased postural sway when viewing optic flow than a stationary stimulus.

Postural sway was greater in patients with complaints of visual vertigo than in healthy controls, as measured by NPL of the head and hips in the anterior-posterior direction. Patients with vestibular disorders(Guerraz et al., 2001; Redfern & Furman, 1994), migraine-related dizziness,(Furman et al., 2005) visual vertigo,(Bronstein, 1995; Guerraz et al., 2001; E. A. Keshner et al., 2007; Pavlou et al., 2006), visual vestibular mismatch,(Van Ombergen et al., 2016) visual sensitivity,(Keshner & Dhaher, 2008), phobic postural vertigo,(Krafczyk, Schlamp, Dieterich, Haberhauer, & Brandt, 1999) and space and motion discomfort(Jacob et al., 1995) have also displayed greater sway than healthy controls. Unlike Jacob et al., persistence of increased postural sway after optic flow periods was not observed.

Both the patients with visual vertigo and the healthy controls had greater anterior-posterior NPL and RMS head movements during optic flow than stationary surround periods. The patients showed larger head sway responses to optic flow than the healthy controls. Keshner et al. also found larger values for RMS head movements during pitch optic flow in patients (n = 4) with visual vertigo in comparison to healthy controls.(Keshner et al., 2007) They also found larger values for RMS head movements and larger delays initiating compensatory head movements during pitch optic flow in patients with visual sensitivity (n = 3) in comparison to healthy controls.(Keshner & Dhaher, 2008) These larger and more delayed head movements indicated that the small sample of patients were more visually dependent.(Keshner & Dhaher, 2008)

Although the type of optic flow (linear versus pitch) and surface (fixed or sway referenced versus rotating or translating) differed between our study and those of Keshner and

colleagues, the findings were consistent. Similarly, patients with visual vertigo also have larger sway path length and RMS head movements than healthy controls during roll optic flow.(Guerraz et al., 2001) Patients with visual vertigo display larger head movements than healthy controls in response to pitch, roll, and anterior-posterior optic flow. Older adults with unilateral vestibular hypofunction had similar magnitude head sway ratios (ratio of head sway during optic flow to head sway during baseline) as healthy older adults.(Sparto et al., 2006) The patients in the study by Sparto et al. had lower DHI scores (M 21.33, SD 14.66) and only 2 of 9 had an abnormal asymmetry on rotational testing, indicating that they had likely compensated for their unilateral vestibular hypofunction.(Sparto et al., 2006) Our subjects were much more symptomatic and had not likely compensated for their vestibular impairments, likely leading to the main effect for group observed for anterior-posterior NPL movement of the head during optic flow.

Both the patients with visual vertigo and the healthy controls had greater anterior-posterior NPL hip movements during optic flow than stationary surround periods. The patients showed larger hip sway responses to optic flow than the healthy controls. Similar to the head movements seen in response to pitch optic flow, Keshner et al. also observed larger values for RMS trunk movements in patients with visual vertigo in comparison to healthy controls.(Keshner et al., 2007) All subjects displayed greater anterior-posterior RMS hip movements during sway-referenced than fixed floor and optic flow than stationary surround periods. The observed responses are due to the moving visual and platform conditions, and are not different between patients with visual vertigo and healthy controls.

All subjects displayed greater medial-lateral NPL and RMS head movements during optic flow than stationary surround periods. All of the values were very small (less than 1 cm/s for

NPL or 1 cm for RMS). Similar values for medial-lateral RMS head movements were obtained (all less than 0.5 cm), with greater sway during the sway-referenced than the fixed floor conditions. All subjects also displayed greater medial-lateral NPL and RMS hip movements during optic flow than stationary surround periods. All of the values were very small (less than 0.5 cm/s for NPL or 0.5 cm for RMS). Similar values for medial-lateral RMS hip movements were obtained (all less than 0.5 cm), with greater sway during the sway-referenced than the fixed floor conditions. The small values for medial-lateral sway are not surprising given that the movement of the visual surround and platform was anterior-posterior and not medial-lateral. The subtle medial-lateral responses observed are due to the moving visual and platform conditions, and are not different between patients with visual vertigo and healthy controls.

All subjects displayed greater anterior-posterior NPL movement of the COP during optic flow periods than stationary surround periods. Both the patients with visual vertigo and the healthy controls had greater anterior-posterior RMS movement of the COP during optic flow periods than stationary surround periods. The anterior-posterior RMS movement of the COP during optic flow periods and stationary surround periods was larger in the patients with visual vertigo than in the healthy controls. This is consistent with the larger sway path length and RMS movement of the COP during roll optic flow in patients with visual vertigo in comparison to healthy controls.(Guerraz et al., 2001)

Bronstein reported that the sway path of the COP was similar for healthy controls, vestibular controls (those with unilateral labyrinthectomy or vestibular neurectomy without visual vertigo), and those with visual vertigo.(Bronstein, 1995) Among those with visual vertigo that had increased postural sway (n = 5), two had central disorders and four had oculomotor abnormalities.(Bronstein, 1995) While our subjects were free of oculomotor abnormalities, eight

of the patients had a definitive or suspected central vestibular disorder. The larger anterior-posterior RMS movement of the COP in the patient group may be explained by increased visual dependence and resulting unsteadiness from central vestibular disorders that impair sensory reweighting and integration.

All subjects displayed greater medial-lateral NPL and RMS movement of the COP during optic flow periods than stationary surround periods. All of the values were very small (less than 1 cm/s for NPL or 1 cm for RMS), which again is expected given that the movement of the visual surround and platform was anterior-posterior and not medial-lateral. The subtle medial-lateral responses observed are due to the moving visual and platform conditions, and are not different between patients with visual vertigo and healthy controls.

The third specific aim of this study was exploratory, and sought to examine the effect of standing on a fixed and sway-referenced surface on cerebral activation during optic flow in patients with complaints of visual vertigo and healthy adults. There were two hypotheses related to this specific aim. First, cerebral activation in the bilateral temporal and occipital lobes would be greater in patients with complaints of visual vertigo than in healthy adults. Second, cerebral activation in the bilateral temporal and occipital lobes would be greater standing on a sway-referenced than a fixed surface.

While standing on a platform that changes from fixed to sway-referenced in the presence of a stationary visual surround, the patients displayed greater activation in the right posterior temporal region than the healthy controls. While the patients displayed activation of all temporal and occipital regions of interest, the largest activation was in the right posterior region. All of these activations, however, were less robust than those seen in the healthy controls, with the exception of the right posterior temporal region. This large increase of HbO_2 in the right

posterior temporal region suggests that the patient group was attempting to maximize the integration of vestibular information for the maintenance of standing balance. This is not surprising, given their known vestibular impairment and the degraded proprioceptive information provided by the changing platform surface. A similar response in the right temporo-parietal region was observed in older adults during computerized dynamic posturography testing during which the platform also changed from fixed to sway-referenced and back to fixed.(Lin et al., 2017) The lack of a difference in the occipital regions of interest indicate that the patients and the healthy controls had similar integration of visual information.

The fourth specific aim of this study was exploratory, and sought to examine the effect of standing on a fixed and sway-referenced surface on postural sway during optic flow in patients with complaints of visual vertigo and healthy adults. There were two hypotheses related to this specific aim. First, postural sway would be greater in patients with complaints of visual vertigo than in healthy adults. Second, postural sway would be greater standing on a sway-referenced than a fixed surface.

Consistently, all outcome measures revealed increased sway during the sway-referenced floor periods in comparison to the fixed floor periods. This increased sway is reflective of the increased balance challenge during the sway-referenced task which compromises proprioceptive information. During single sine anterior-posterior optic flow, head sway was 2.5-3.2 times greater when standing on a sway-referenced in comparison to a fixed surfaced.(Sparto et al., 2006) Increased sway when standing on a sway-referenced in comparison to a fixed surface is well established in the literature.(Borger et al., 1999; Peterka & Benolken, 1995)

There were, however, no differences in sway between the patients and healthy controls during the changing platform condition. Many of the patients reported that they did not find this

exploratory condition particularly challenging. While the condition was meant to simulate getting on and off an escalator or elevator, many patients felt more bothered by the optical flow and complex visual stimuli and not the change in surface condition during these situations. The lack of a difference between groups indicates that the patients were able to successfully integrate afferent information and generate an appropriate motor response.

This is the first study to apply functional brain imaging during a standing balance task in patients with visual vertigo in comparison to healthy adults. The patients had a variety of central and/or peripheral vestibular disorders, typical of those referred for vestibular physical therapy. The results of the study can be generalized to patients presenting for outpatient vestibular physical therapy who present with complaints of visual vertigo. The use of fNIRS provided a means to record changes in cortical activation while the subjects performed a standing balance task. The design of the probe in a neoprene head cap allowed sources and detectors to make firm contact with the scalp, decreasing motion artifacts and limiting noise in optical signals. Few studies have used fNIRS over the occipital regions due to hair, increased thickness of the skull, and presence of the dural sinuses. The occipital regions of interest were key to exploring the visual-vestibular interaction, and this study, like that of Lin et al.,(Lin et al., 2017) demonstrates that fNIRS can be used to image this region.

A limitation of the study was that the proprioception of the participants was not assessed during the screening visit. The screening visit did include a brief screening for pin prick, light touch, and assessment with Semmes-Weinstein monofilaments for protective sensation. Additionally, a Rydel-Seiffer tuning fork was used to assess vibration sensation. It is unlikely that the patients had gross deficits in proprioception based on their observed performance during clinical gait and balance assessments. However, it is not known if the decreased activation of the

bilateral anterior temporal regions in the patients observed during fixed surface conditions could be the result of absent or impaired proprioceptive information necessary for balance. The decreased cortical activation in the superior temporal gyrus, a region of sensory-motor integration, could indicate decreased weighting of somatosensory information due to diminished afferent proprioceptive input. Additionally, the limited depth of fNIRS measurements limits this study to recording changes from cortical areas. Changes from deeper areas involved in processing visual and vestibular information cannot be measured.

Another limitation of the study was that the effect of anxiety was not included as a covariate in the fNIRS or postural sway analyses. Decreased activity and functional connectivity of the anterior insula and anterior cingulate cortex (regions of anxiety modulation) and the PIVC has been noted in individuals with chronic subjective dizziness.(Indovina et al., 2015) It is not known if the decreased activation of the bilateral anterior temporal regions in the patients observed during fixed surface conditions was modulated by worse anxiety scores. Patients with greater anxiety also display more higher-frequency/lower-amplitude postural sway.(Krafczyk et al., 1999) Sparto et al. have described a statistical test using an *F*-statistic to investigate if there is significant power in postural data at a particular frequency.(Sparto, Jasko, & Loughlin, 2004) It would be interesting to compare patients with visual vertigo and healthy controls in the higher frequency range of the power spectrum.

Future work could compare patients with particular diagnoses (such as vestibular migraine and unilateral vestibular hypofunction). Patients with central and peripheral vestibular disorders may process visual information for balance differently. It would also be interesting to explore if there is a difference in cortical activation in those with complaints of visual vertigo that are acute (uncompensated) versus those that are chronic (poorly compensated) or recovered

(mostly compensated). Additionally, future studies could assess if the observed differences in cortical activation seen in this study normalize in the patient group following physical therapy intervention. Dose is critical for treatment effectiveness, and physical therapists need sound evidence on which to base decisions for frequency, intensity, and timing of habituation exercises. All of these treatment parameters could be explored, using fNIRS to monitor recovery.

4.5 CONCLUSION

Functional NIRS was used to record changes in cortical activation in subjects with complaints of visual vertigo and healthy controls while they viewed anterior-posterior optic flow. Cortical activation was decreased in patients in comparison to healthy controls in the bilateral anterior temporal regions when single and sum of sines optic flow was viewed while standing on a fixed surface. Cortical activation was also decreased in the right anterior temporal region when sum of sines optic flow was viewed while standing on a sway-referenced surface. These changes may indicate decreased sensory integration, as patients with visual vertigo had increased anterior-posterior movement of the head and hips in comparison to healthy controls. Future work should explore if this same cortical activation pattern can be modified with physical therapy intervention, such as habituation exercises using optic flow. Functional NIRS, a non-invasive neuroimaging modality, is appropriate for exploring the relationships among optic flow, standing balance, and cerebral activation.

5.0 CONCLUSIONS

This study was performed to better understand the processing of optic flow information and the relationship between optic flow and postural control. Changes in cerebral activation during exposure to a visual stimulus designed to induce vection (optic flow in the yaw plane) was explored in healthy adults during quiet stance. Differences in cerebral activation between healthy adults and patients with visual vertigo during exposure to anterior-posterior optic flow while standing on a fixed or sway-referenced surface was explored. Study of the relationship between optic flow and postural control during quiet stance was conducted by measuring postural sway. Functional NIRS, a non-invasive neuroimaging modality, was found to be appropriate for exploring the relationships among optic flow, perception of vection, standing balance, and cerebral activation.

During unidirectional optic flow in the yaw plane viewed with a fixation cross, there was increased activation in the bilateral fronto-temporo-parietal lobes in the region of the supramarginal gyrus. This region is involved in sensory reweighting of visual, vestibular, and proprioceptive system information.(Karim et al., 2013) Fixation is known to enhance the perception of vection. Previous research found that the presence of a fixation cross during linear left to right optic flow decreased vection latencies and increased vection duration.(Tarita-Nistor et al., 2006) Decreased vection latencies were also found with fixation compared to without fixation during yaw and pitch optic flow.(Fushiki et al., 2000) Enhanced perception of vection

may be explained by suppression of optokinetic nystagmus, which causes the visual stimuli to repeatedly move across the retina.(Tarita-Nistor et al., 2006) This may lead to greater afferent input for central processing in cortical regions responsive to visual motion and optic flow information as well as regions involved in multi-sensory integration.

The MSAQ was originally developed to assess motion sickness as a multidimensional construct,(Gianaros et al., 2001) but was used in this study to quantify vection. In this sample of 15 healthy adults, no difference was found in subjective ratings of vection intensity using the MSAQ when the optic flow stimulus was viewed with and without the presence of a fixation cross. This suggests that item 14 of the MSAQ may not be sensitive to changes in perception of vection intensity. Though subjective ratings of vection intensity were not different, cerebral activation was different with and without a fixation cross. This may indicate that fNIRS provides a more sensitive measure of perception of vection intensity. Given the limitations of self-report measures of vection and need for objective measures of vection,(Palmisano et al., 2015) fNIRS may be a useful tool for indicating the conscious perception of self-motion.

In healthy subjects, cortical activation was greater when optic flow moving unidirectionally in the yaw plane was viewed with a fixation cross. With fixation, greater activation was seen in the bilateral fronto-temporo-parietal lobes. While optokinetic stimuli are often utilized by physical therapists during vestibular rehabilitation therapy, evidence-based stimulus parameters for delivery of optokinetic stimuli are not yet known. Greater cortical activation in the bilateral fronto-temporo-parietal lobes provides preliminary support for the use of a fixation cross during habituation to optic flow.

fNIRS was used to investigate cortical activity in patients with visual vertigo and healthy controls during single sine and sum of sines optic flow while standing on a fixed or sway-

referenced surface. The primary finding was decreased activation in the bilateral anterior temporal regions in the patient group when viewing optic flow while standing on a fixed surface in comparison to the healthy controls. Decreased activation was also seen in the right anterior temporal region in the patient group when viewing sum of sines optic flow while standing on a sway-referenced surface in comparison to the healthy controls. Patients with visual vertigo show less cerebral activation in regions associated with multi-sensory integration in comparison to healthy controls. This is similar to the results of Indovina et al., who found that patients with chronic subjective dizziness showed activation to a lesser extent in the superior temporal gyrus in comparison to healthy controls.(Indovina et al., 2015) In an fMRI study of patients with unilateral vestibular neurectomies, a similar pattern of activation to a lesser extent was seen in the patients in comparison to healthy controls.(Deutschländer et al., 2008) This decreased activation may represent an altered ability to perform sensory re-weighting of visual and vestibular information, leading to symptoms of dizziness and imbalance.

Postural sway was greater in patients with complaints of visual vertigo than in healthy controls, as measured by NPL of the head and hips in the anterior-posterior direction. The patients showed larger head sway responses to optic flow than the healthy controls. Larger values for RMS head movements during pitch optic flow in patients with visual vertigo and visual sensitivity have been reported. (Keshner & Dhaher, 2008; Keshner et al., 2007) Patients with visual vertigo also had larger sway path length and RMS head movements than healthy controls during roll optic flow.(Guerraz et al., 2001) These larger head movements indicated that the small sample of patients were more visually dependent.(Keshner & Dhaher, 2008) Similarly, the greater sway observed in our patients during optic flow periods indicated greater sensory weighting of visual information for balance. The increased NPL anterior-posterior

movement of the hips in our patients with visual vertigo during optic flow was similar to the larger values for RMS trunk movements in patients with visual vertigo during optic flow.(Keshner et al., 2007) Anterior-posterior RMS movement of the COP during optic flow periods and stationary surround periods was larger in the patients with visual vertigo than in the healthy controls. This was also consistent with the larger sway path length and RMS movement of the COP during roll optic flow in patients with visual vertigo in comparison to healthy controls.(Guerraz et al., 2001)

In comparison to healthy controls, patients with visual vertigo had decreased cortical activation in the bilateral anterior temporal regions when single and sum of sines optic flow was viewed while standing on a fixed surface. Patients with visual vertigo also had decreased cortical activation in the right posterior temporal region, in comparison to healthy controls, when sum of sines optic flow was viewed while standing on a fixed surface. These changes may indicate decreased sensory integration, as patients with visual vertigo had increased anterior-posterior movement of the head and hips in comparison to healthy controls during periods of optic flow. Future work should explore if this cortical activation pattern and postural imbalance can be modified with physical therapy intervention, such as habituation exercises using optic flow.

APPENDIX A

HEADACHE DIAGNOSTIC INTERVIEW FOR DETERMINATION OF MIGRAINE

The following is the Migraine Assessment Tool, as originally published by Marcus et al.(Marcus, Kapelewski, Jacob, Rudy, & Furman, 2004)

1. Did the headaches start within 2 weeks of a head injury, trauma, or medical illness?

   YES (If yes, **STOP**) **NO** (If no, proceed to next question)

2. Do you have any brain abnormality, like tumors or hydrocephalus?

   YES (If yes, **STOP**) **NO** (If no, proceed to next question)

3. Do you have a headache every day or take over-the-counter or prescription pain or headache medications (e.g. Excedrin) more than 4 days per week?

   YES (If yes, **STOP**) **NO** (If no, proceed to next question)

4. Do you have an intermittent or constant headache?

   CONSTANT (If constant, **STOP**) **INTERMITTENT** (If no, proceed to next question)

5. How long does each individual headache episode last?

   < 2 hours (If <2 hours, **STOP**) $\geq$ 2 hours (If $\geq$ 2 hours, proceed to next question)

6. Do you have **any** of the following neurological symptoms immediately before or during your headache episodes?

   _____Visual scotoma (area where vision is diminished)
   _____Visual hallucination (zig-zag or wavy lines, colored lights or balls, shimmering patterns)
   _____Weakness or numbness on one side of your body

   If **YES**, diagnose **MIGRAINE**. No further questions needed.
   If **NO**, proceed with question # 7

7. Do you have at least **2** of the following symptoms with your headache?

_____Pain is on one side of the head during a headache episode
_____Pain feels like throbbing or pulsing sensation
_____Pain limits, restricts, or interferes with routine activities
_____Pain is made worse by performing routine activities, such as stair climbing

NO (**STOP!** No diagnosis of migraine) **YES** (If yes, proceed to next question)

8. Do you have at least **1** of the following symptoms with your headache?

_____Nausea or vomiting
_____ Markedly increased sensitivity to **BOTH** normal room lighting **AND** conversational speech (The person should report a need to turn down or off lights, close curtains or blinds, turn down or off radio or television, or need to retreat to dark, quiet room.)

If **YES,** then diagnose **MIGRAINE**. If **NO**, no diagnosis of migraine.

APPENDIX B

MOTION SICKNESS SUSCEPTIBILITY QUESTIONNAIRE

The following is the Motion Sickness Susceptibility Questionnaire revised, as originally published by Golding et al.(Golding, 1998) If the subject has never experienced the type of transport or entertainment they tick the box in the column labeled "Never."

This questionnaire is designed to find out how susceptible to motion sickness you are and what sorts of motion are most effective in causing that sickness. Sickness here means feeling queasy or nauseated or actually vomiting.

After some background questions, the questionnaire consists of two sections:

Section A is concerned with your **childhood** experiences of travel and motion sickness, that is, before the age of 12 years.

Section B is concerned with your experiences of travel and motion sickness **over the last 10 years**.

The correct way to answer each question is explained in the body of the questionnaire. It is important that you answer every question.

Thank you for your help.

Background Questions

1. Please State Your Age _____ Years

2. Please State Your Sex (tick box) Male Female

[ ] [ ]

1 2

3. Please State Your Current Occupation _____

4. Do you regard yourself as susceptible to motion sickness? (tick box)

Not at all Slightly Moderately Very much so

[ ] [ ] [ ] [ ]

0 1 2 3

Section A: **Your CHILDHOOD Experience Only** (before 12 years of age)

For each of the following types of transport or entertainment please indicate:

5. As a **Child (before age 12)**, how often you **Travelled or Experienced** (tick boxes):

	Never	1 to 4 trips	5 to 10 trips	11 or more trips
Cars				
Buses or Coaches				
Trains				
Aircraft				
Small Boats				
Ships, e.g. Channel Ferries				
Swings				
Roundabouts: playgrounds				
Big Dippers, Funfair Rides				
	0	1	2	3

6. As a **Child (before age 12)**, how often you **Felt Sick or Nauseated** (tick boxes):

	Never	Rarely	Sometimes	Frequently	Always
Cars					
Buses or Coaches					
Trains					
Aircraft					
Small Boats					
Ships, e.g. Channel Ferries					
Swings					
Roundabouts: playgrounds					
Big Dippers, Funfair Rides					
	0	1	2	3	4

7. As a **Child (before age 12)**, how often you **Vomited** (tick boxes):

	Never	Rarely	Sometimes	Frequently	Always
Cars					
Buses or Coaches					
Trains					
Aircraft					
Small Boats					
Ships, e.g. Channel Ferries					
Swings					
Roundabouts: playgrounds					
Big Dippers, Funfair Rides					
	0	1	2	3	4

Section B: **Your Experience over the Last 10 Years (approximately).**

For each of the following types of transport or entertainment please indicate:

8. Over the **last 10 years**, how often you **Travelled** or **Experienced** (tick boxes):

	Never	1 to 4 trips	5 to 10 trips	11 or more trips
Cars				
Buses or Coaches				
Trains				
Aircraft				
Small Boats				
Ships, e.g. Channel Ferries				
Swings				
Roundabouts: playgrounds				
Big Dippers, Funfair Rides				
	0	1	2	3

9. Over the **last 10 years**, how often you **Felt Sick** or **Nauseated** (tick boxes):

	Never	Rarely	Sometimes	Frequently	Always
Cars					
Buses or Coaches					
Trains					
Aircraft					
Small Boats					
Ships, e.g. Channel Ferries					
Swings					
Roundabouts: playgrounds					
Big Dippers, Funfair Rides					
	0	1	2	3	4

10. Over the **last 10 years**, how often you **Vomited** (tick boxes):

	Never	Rarely	Sometimes	Frequently	Always
Cars					
Buses or Coaches					
Trains					
Aircraft					
Small Boats					
Ships, e.g. Channel Ferries					
Swings					
Roundabouts: playgrounds					
Big Dippers, Funfair Rides					
	0	1	2	3	4

APPENDIX C

MOTION SICKNESS ASSESSMENT QUESTIONNAIRE AND HANDOUTS

The following is the Motion Sickness Assessment Questionnaire (MSAQ), as originally published by Gianaros et al.(Gianaros et al., 2001)

***Instructions*. Using the scale below, please rate how accurately the following statements describe your experience**

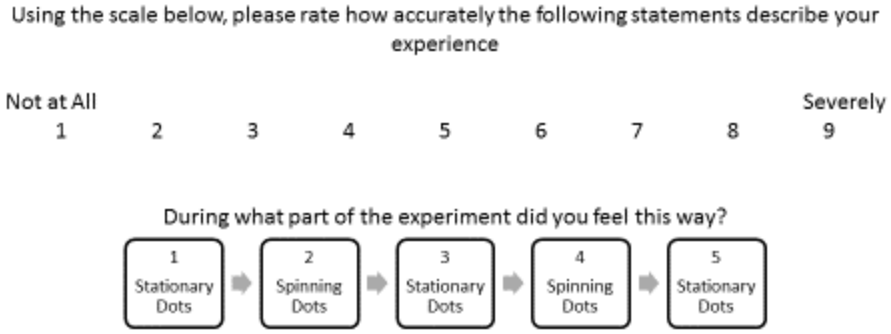
Not at all Severely

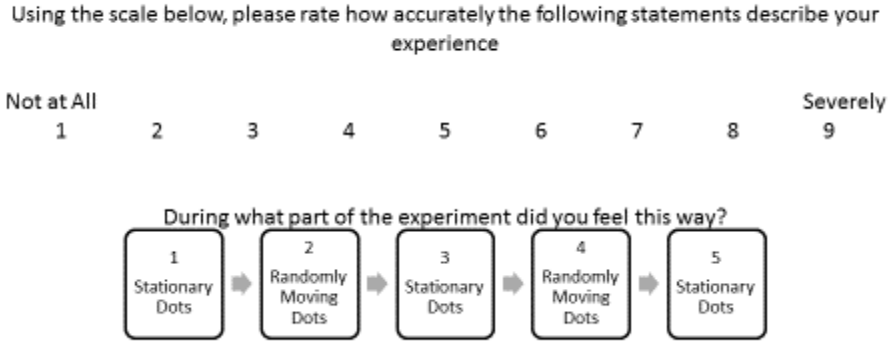
1-----2-----3-----4-----5-----6-----7-----8-----9

1. I felt sick to my stomach (G)	9. I felt disoriented (Q)
2. I felt faint-like (C)	10. I felt tired/fatigued (S)
3. I felt annoyed/irritated (S)	11. I felt nauseated (G)
4. I felt sweaty (P)	12. I felt hot/warm (P)
5. I felt queasy (P)	13. I felt dizzy (C)
6. I felt lightheaded (C)	14. I felt like I was spinning (C)
7. I felt drowsy (S)	15. I felt as if I may vomit (G)
8. I felt clammy/cold sweat (P)	16. I felt uneasy (S)

Note. G; Gastrointestinal; C: Central; P: Peripheral; SR; Sopite-related.

The two handouts below were provided to subjects after each trial to aid in clarifying the rating scale for the MSAQ items. The investigator read each of the 16 statements from the MSAQ above, and asked the subject for a number (ranging 1 to 9) for severity. If the subject responded with a 2 or higher, the investigator further probed by asking the subject during what part of the experiment they felt the motion sickness symptom. If the subject had symptoms during more than one part of the experiment (depicted in squares 1-5), severity ratings were recorded for each part of the experiment that were symptom-provoking. The graphic depicting the ABABA phases of the trial helped subjects identify when they perceived their symptoms during the course of the trial.

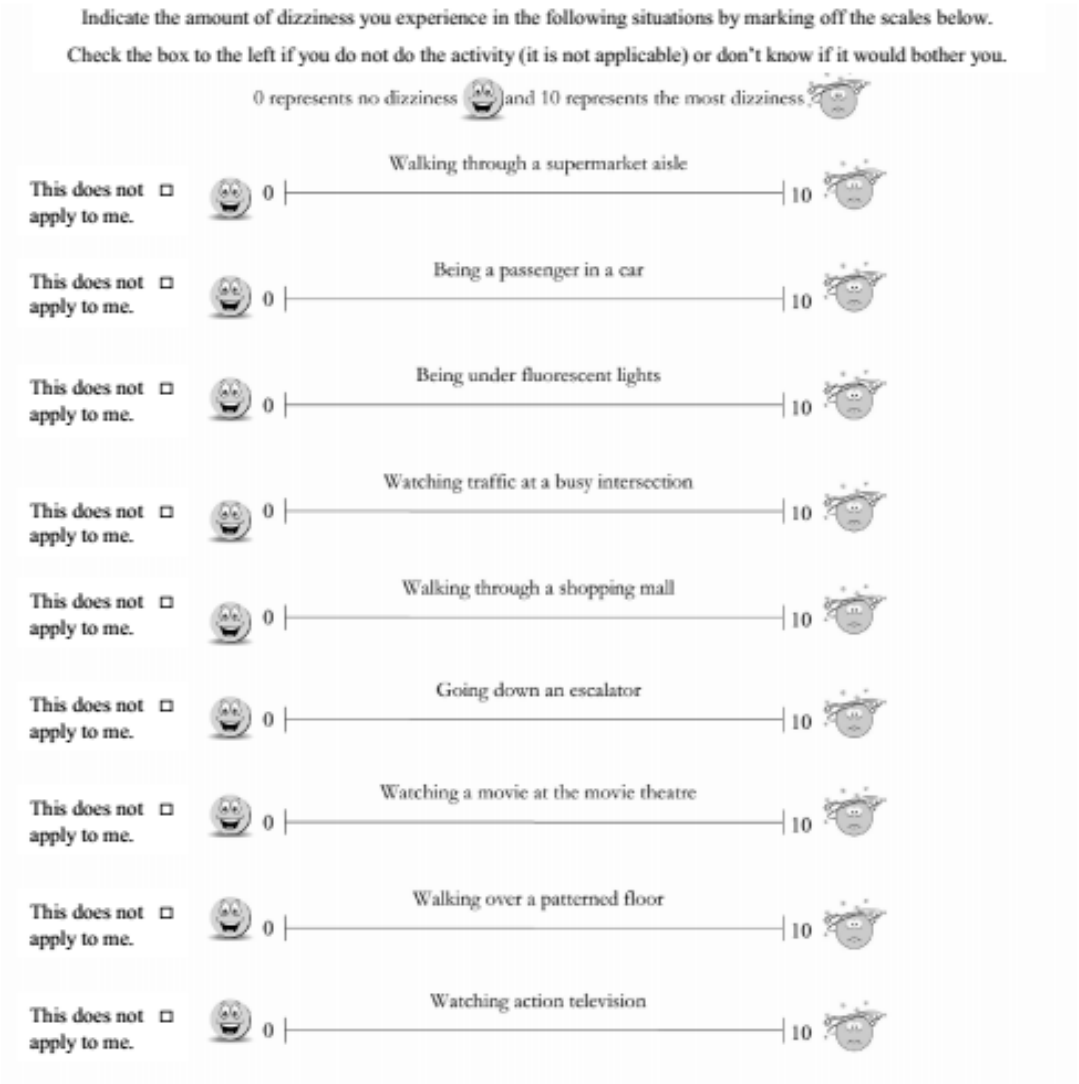




APPENDIX D

VISUAL VERTIGO ANALOGUE SCALE

The following is the Visual Vertigo Analogue Scale (VVAS), adapted from Dannenbaum et al.(Dannenbaum et al., 2011)



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