Changes in cerebral activation in individuals with and without visual vertigo during optic flow: A functional near-infrared spectroscopy study

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ABSTRACT

Background and purpose: Individuals with visual vertigo (VV) 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 to treat these symptoms, but it is not known how individuals with VV process the visual stimuli. The primary purpose of this study was to use functional near-infrared spectroscopy (fNIRS) to determine if individuals with VV have different cerebral activation during optic flow compared with control subjects.
Methods: Fifteen individuals (5 males and 10 females in each group) with VV seeking care for dizziness and 15 healthy controls (CON) stood in a virtual reality environment and viewed anterior-posterior optic flow. The support surface was either fixed or sway-referenced. Changes in cerebral activation were recorded using fNIRS during periods of optic flow relative to a stationary visual environment. Postural sway of the head and center of mass was recorded using an electromagnetic tracker.
Results: Compared with CON, the VV group displayed decreased activation in the bilateral middle frontal regions when viewing optic flow while standing on a fixed platform. Despite both groups having significantly increased activation in most regions while viewing optic flow on a sway-referenced surface, the VV group did not have as much of an increase in the right middle frontal region when viewing unpredictable optic flow in comparison with the CON group.
Discussion and conclusions: Individuals with VV produced a pattern of reduced middle frontal cerebral activation when viewing optic flow compared with CON. Decreased activation in the middle frontal regions of the cerebral cortex may represent an alteration in control over the normal reciprocal inhibitory visual-vestibular interaction in visually dependent individuals. Although preliminary, these findings add to a growing body of literature using functional brain imaging to explore changes in cerebral activation in individuals with complaints of dizziness, disorientation, and unsteadiness. Future studies in larger samples should explore if this decreased activation is modified following a rehabilitation regimen consisting of visual habituation exercises.

1. Introduction

Visual vertigo (VV) 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 VV are highly visually dependent (Bronstein, 1995), giving greater weight to visual information for the

maintenance of balance. These visually dependent individuals may display increased postural sway with full-field visual motion stimuli (Bronstein, 1995; Rábago and Wilken, 2011).

The pathophysiology underlying VV is not well understood. During resting state functional magnetic resonance imaging (fMRI), individuals with visually induced dizziness had decreased functional connectivity in the right superior temporal gyrus, likely indicative of decreased weighting and sensory integration (cortical-level processing) of vestibular information at rest (Van Ombergen et al., 2017). Individuals with dizziness and VV also have more nonspecific hemispheric white

matter abnormalities (hyperintensities) than individuals with dizziness without VV (Pollak et al., 2015).

Two fMRI studies have noted differences in brain activation between patients with unilateral vestibular neurectomy or chronic subjective dizziness and healthy controls (Indovina et al., 2015; Deutschländer et al., 2008). Individuals with chronic subjective dizziness and healthy controls both responded strongly in the superior temporal gyrus to sound-evoked vestibular stimuli (loud short tone bursts), while patients with chronic subjective dizziness had less cerebral activation in several areas, including the right posterior insula and superior temporal gyrus, left anterior insula, inferior frontal gyrus and anterior cingulate cortex, and bilateral hippocampus (Indovina et al., 2015). A similar pattern of reduced activation was seen in patients with unilateral vestibular neurectomy in comparison to healthy controls in response to narrow field-of-view optokinetic visual motion stimuli, with reduced activity in the posterior insula, superior temporal gyrus, and hippocampus (Deutschländer et al., 2008). Although visually-evoked symptoms are elicited in individuals with VV, it has not been investigated if they also generate abnormal patterns of cerebral activation in response to full-field visual motion stimuli. Because fMRI requires that the participant lie supine and motionless during imaging, it precludes assessment of how vestibular and visual stimuli affect upright balance tasks.

Optic flow is the continual change of images on the retina that occurs from movement of the visual environment, and provides important afferent information for control of posture and gait speed (Lappe, 2009). Optic flow, in the form of visual habituation exercises, is often prescribed to patients with VV. These habituation exercises have been shown to decrease VV symptoms when incorporated into rehabilitation regimens (Pavlou et al., 2013; Pavlou et al., 2004). While optic flow stimuli are often utilized by clinicians, evidence-based stimulus parameters are not yet known and its mechanisms are poorly understood. Therefore, understanding the cerebral responses to optic flow stimuli may help to elucidate these mechanisms and help us to better define the stimulus parameters needed to optimize rehabilitation. The primary purpose of this study was to determine if individuals with VV have different cerebral activation during optic flow compared with control subjects.

2. Material and methods

2.1. Participants

Thirty participants between the ages of 18 and 65 years old were included in the study. All participants were right-handed, as determined by the Edinburgh Handedness Inventory-Short Form (Veale, 2014). Individuals with VV were included after being evaluated by a board-certified neurologist, who made a determination based on the findings of the qualitative and quantitative examination. In addition, the individuals with VV had to rate at least two of the nine items on the Visual Vertigo Analogue Scale (VVAS) above zero (VVAS positive) (Dannenbaum et al., 2011), and report a score of 31 or greater on the Dizziness Handicap Inventory (DHI), indicating a moderate handicap (Whitney et al., 2004). Scores on the VVAS range from 0 (no VV) to 100 (severe VV) (Dannenbaum et al., 2011). Healthy men and women served as near age- (within three years of the patient's age) and gender-matched controls (CON).

Subjects were ineligible to participate in the study if they had: corrected binocular visual acuity worse than 20/40, macular degeneration, or glaucoma; unwillingness to abstain from alcohol for 48 h prior to testing; known pregnancy; and/or body weight > 118 kg. Additionally, CON were ineligible to participate in the study if they had a: history of otologic or neurologic disease; history of migraine; or abnormal vestibular function tests. Individuals with VV using medications that may have affected balance or cerebral blood flow were tested at least 48 h after taking the last dose. Written informed consent was obtained from all participants and the study was approved by the University of Pittsburgh Institutional Review Board. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Experimental design

A cross-sectional experimental study consisting of four combinations of two anterior-posterior (AP) optic flow stimulation frequencies (single sine and sum of sines) and two platform conditions (fixed and sway-referenced) was performed. Each of the four combinations were performed twice for a total of eight trials during a single visit. During each trial, a blocked design (e.g., A-B-A-B-A) was employed, where A was comprised of a stationary visual field and B was comprised of one of the two types of AP optic flow stimulation frequencies. As part of the A-B-A-B-A design, each block was presented for 36 s for a total of 3 min for each trial. While viewing the visual stimuli, participants stood on a fixed or sway-referenced platform during the entire trial. 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. The order of the first four trials was randomly assigned, and this order was repeated a second time.

2.3. Visual stimuli

The visual stimulus was back-projected onto a three-screen wide field-of-view (180° horizontal and 70° vertical display). Participants faced the front screen that was 1.5 m away (Fig. 1). An AP optic flow stimulus was selected to simulate the "moving room" paradigm used in previous research (Haibach et al., 2008; Stoffregen and Smart, 1998; Haibach et al., 2009; Schmuckler, 1997). The structure of the optic flow was designed to evoke a strong postural response (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 a bullseye pattern of alternating black and white rings on the front screen to provide radial optic flow in the central field of view. For AP 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, peak amplitude: 3.76 cm, 4.88 cm, 6.39 cm, respectively). Both stimuli had an RMS velocity of 8.88 cm/s. The sum of three sines was used to produce changes in the scene velocity that would be difficult to anticipate (Andersen and Dyre, 1989). The baseline (control) condition was a stationary bullseye and checkerboard.

2.4. Measurements

2.4.1. Cerebral activation: near-infrared spectroscopy

fNIRS is a non-invasive functional neuroimaging method that measures changes in the volume and oxygenation of blood. fNIRS allows for imaging during functional tasks such as standing balance and gait. During imaging, flexible fiber optic cables deliver low levels of light (< 0.4 W/cm^2) to sources on the scalp. This light diffuses through the tissues to a depth of approximately 5–8 mm in the outer cerebral cortex (Boas and Dale, 2005). Light that is not absorbed is detected and flexible fiber optic cables carry the light back to photon detectors within the fNIRS instrument. The change in intensity of visible red to near-infrared light between sources and detectors that are placed on the scalp is measured. During task performance, regional changes in oxy-hemoglobin (HbO$_2$) and deoxyhemoglobin (Hb) concentration change the absorption of light in the brain.

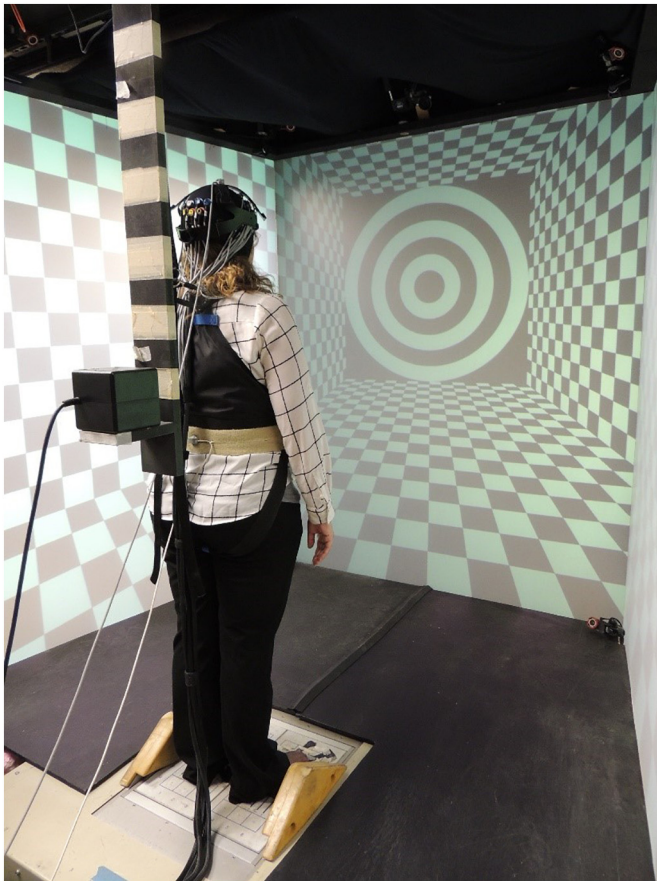A 32-channel continuous wave fNIRS instrument (CW6 Real-time

Fig. 1. The participant was exposed to two types of anterior-posterior optic flow while standing in a three-screen wide field-of-view virtual reality environment.

system; TechEn, Inc.; Milford, MA) was used to record changes in HbO_2 and Hb concentration at 830 nm and 690 nm, respectively (Cope et al., 1988; Strangman et al., 2003). A fNIRS head cap consisting of 11 sources and 20 detectors located over the bilateral temporal and occipital lobes was used (Fig. 2) to assess three regions of interest: middle frontal gyrus, superior temporal gyrus, and extrastriate visual cortical regions. Although these regions of interest are defined by the centroid of the sources, the middle frontal region spans an area from the superior frontal gyrus to the inferior frontal gyrus, and the superior temporal region spans an area from the inferior frontal gyrus to the middle temporal gyrus. These regions were studied because of their relevance to visual and vestibular stimulation reported in previous studies (Van Ombergen et al., 2017; Indovina et al., 2015; Bense et al., 2001; Lopez and Blanke, 2011; Stephan et al., 2005; Della-Justina et al., 2015;

Dieterich et al., 2003a). Optical data from 72 source-detector combinations (36 source-detector combinations at two wavelengths) was collected at 20 Hz and down sampled to 4 Hz using a custom-built MATLAB-based acquisition software program (Barker et al., 2013).

Light intensity signals were first converted to changes in optical density over time and then converted to HbO_2 and Hb estimates, as a measure of cerebral activity, via the modified Beer-Lambert law with a partial path length correction of 0.1 for both wavelengths (Strangman et al., 2003).

2.4.2. Postural sway

Participants 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 center of pressure (COP). An electromagnetic tracking system (Polhemus Fastrak, Colchester, VT) was used to record postural sway. Participants wore receivers on top of their head and on a belt placed at the level of the iliac crests to approximate the location of the center of mass (COM). The position of the receivers was measured at a sampling rate of 60 Hz. These postural sway data were used to compute the root mean square (RMS) and normalized path length (NPL) of head, COM, and COP movements.

2.5. Statistical analysis

Demographic and postural data were analyzed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY) and optical data were analyzed using MATLAB (Mathworks, Natick, MA). Descriptive statistics were calculated for demographic variables. Demographic data were checked for normality using Shapiro-Wilk tests, and comparisons were made using dependent *t*-tests or Wilcoxon Signed Ranks tests where appropriate.

2.5.1. Cerebral activation: near-infrared spectroscopy

The time-course of hemoglobin changes for each source-detector pair was analyzed using a general linear model (GLM) $\Delta[Hbx] = X * \beta + \epsilon$ where $\Delta[Hbx]$ is the change in concentration of HbO_2 or Hb, X is the design matrix encoding the timing of stimulus events, and β is the coefficient (weight) of that stimulus condition for that source-detector channel. The design matrix was constructed from the convolution of the stimulus timing and duration with a canonical hemodynamic response function (see details in (Barker et al., 2013)).

In this analysis, no preprocessing was applied. Instead, physiological noise and motion artifacts were dealt with statistically within the GLM (Huppert, 2016). To reduce effects of motion artifacts and systemic physiology, an iteratively auto-regressively whitened, weighted least-squares model was used to solve the general linear equation (Barker et al., 2013). This regression model uses an nth order auto-regressive filter determined by an Akaike model-order selection to whiten both sides of the GLM expression. The regression coefficients (β) and

Fig. 2. The participant wore a fNIRS head cap that consisted of 11 sources (red with capital letters A-K) and 20 detectors (blue with numbers 1–20) on the scalp, distributed between the left temporal (left), occipital (center), and right temporal (right) regions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

their error-covariance (Covβ) are estimated, and used to define statistical tests between task conditions (optic flow) or baseline (stationary visual field). The subject-level analysis to investigate if the optic flow stimulus elicited a significant brain activation compared with the stationary visual field was done using a GLM with a boxcar function of the timing of the optic flow stimulus as a regressor (Barker et al., 2013). The timing of the A-B-A-B-A design was specified in the design matrix. The regression model was solved sequentially for each data file for each participant. All source-detector pairs within a file were solved concurrently yielding a full covariance model of the noise, which was used in group-level analysis. *t*-tests were used to determine if the regression coefficients were statistically non-zero.

For each of the four optic flow frequency and platform combinations, group-level analysis was performed using a linear mixed effects model, using the task-related regression weights (β) from the first-level GLM as the dependent variable and subject 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 (Covβ) of the first level GLM model. To control for multiple comparisons, a false discovery rate (FDR)-correction was used with the significance level set at 0.05 ($q \leq 0.05$) (Benjamini and Hochberg, 1995). Six regions of interest were defined (left and right middle frontal, superior temporal, and occipital). Each of the middle frontal regions of interest, comprised of two sources and six detectors, had eight channels. Each of the superior temporal regions of interest, comprised of two sources and five detectors, had seven channels. The occipital regions of interest, each comprised of two sources and two detectors, each had three channels.

2.5.2. Postural sway

Anterior-posterior (AP) and medial-lateral (ML) translation data from the electromagnetic trackers on the head and COM, and AP and ML COP data from the force plate were digitally low-pass filtered using zero-phase implementation of a fourth order Butterworth filter with a cutoff frequency of 2 Hz. Filtered data were then used to calculate the RMS and NPL of the postural sway measures. 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), the mean values for the dependent variables were combined for period and condition to reduce the number of variables. Linear mixed effects models were used to test for differences between groups (VV versus CON), platform and optic flow frequency 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). Interaction effects were group*condition, group*period, and condition*period. Subject was included as a random effect. Post-hoc testing of the estimated marginal means consisted of pairwise comparisons using the Sidak adjustment. A restricted maximum likelihood approach was used.

3. Results

The individuals with VV were diagnosed by a board-certified neurologist as having a variety of central and/or peripheral vestibular disorders (Table 1). While all of the individuals with VV were VVAS positive[12], only one individual met all five of the diagnostic criteria for persistent postural-perceptual dizziness introduced in the consensus document of the committee for the Classification of Vestibular Disorders of the Barany Society (Staab et al., 2017). The VV group's mean score on the VVAS was 58 (SD 21) and 49 (SD 16) on the DHI. There was no difference in age (VV mean 39 years [SD 12], CON mean 38 years [SD 12]), height (VV mean 169 cm [SD 7], CON mean 172 cm [SD 9]), and weight (VV mean 69 kg [SD 12], CON mean 77 kg [SD 17]) between the two groups.

During single sine optic flow while standing on a fixed floor, VV

subjects had no significant differences in cerebral activation (i.e., HbO$_2$ concentration) between the optic flow and stationary visual stimuli periods, but there were several non-significant reductions in activation in the bilateral middle frontal regions and right superior temporal region (Table 2). In CON, increased HbO$_2$ was seen in the bilateral middle frontal regions, and right occipital region, although the left occipital region showed a similar trend. Because of the relative reduction in HbO$_2$ in middle frontal regions of the VV group and relative increase in HbO$_2$ in the same regions of the CON, there was a significant reduction in activation of the left and right middle frontal regions in the VV compared with CON. There were no significant differences in occipital or superior temporal regions between the VV and CON groups.

During sum of sines optic flow while standing on a fixed floor, VV subjects had decreased HbO$_2$ in the left middle frontal region. Increased HbO$_2$ was seen in the left superior temporal region and right occipital region of interest (Table 3). The CON displayed an increase in HbO$_2$ in the bilateral middle frontal regions and in both occipital regions. Again, the relative decrease in HbO$_2$ in the middle frontal regions of the VV combined with the increase in the same regions of the CON resulted in significant relative reductions in middle frontal activation in VV compared with the CON.

There was a substantial increase in cerebral activation across the regions of interest when optic flow was viewed on a sway-referenced platform. In VV, during single sine optic flow while standing on a sway-referenced floor, significantly increased HbO$_2$ was seen in all regions except the right middle frontal region (Table 4). Increased activation was seen in the CON for all regions of interest (Table 4). Due to the similar increase in HbO$_2$ for both groups, there was no difference in the activation between VV and CON in any region.

A comparable pattern of activation to the single sine optic flow, sway-referenced platform condition was observed during the sum of sines optic flow, sway-referenced platform condition (Table 5). The VV group had increased HbO$_2$ in all regions except for the left occipital region. In CON, increased HbO$_2$ was found in all regions of interest. In comparing the VV with CON, the relative activation for VV was less than CON in 4 out of 6 regions, but only the right middle frontal region was significantly reduced.

The movement of the head, COM, and COP were highly correlated and produced similar statistical results; similarly, the NPL and RMS findings were consistent. Therefore, only the AP NPL movement of the head is presented (Fig. 3). Across all periods and conditions, VV had about 38% more head sway NPL than CON, (1.91 versus 1.38 cm/s, $F_{(1,35.6)} = 5.05$, $p = .031$). In addition, all subjects had 89% larger head sway during periods of optic flow, than when the visual surround was stationary, (2.14 versus 1.13 cm/s, $F_{(1,64.4)} = 109.35$, $p < .001$). A significant effect of condition was also observed ($F_{(3,44.9)} = 34.95$, $p < .001$), whereby approximately 2.8 times greater head sway NPL was generated during the sway-referenced platform conditions compared with the fixed platform conditions, but there was no difference between the single and sum-of-sines optic flow stimulation. Importantly, there was a significant interaction between group and optic flow period ($F_{(1,35.5)} = 7.13$, $p = .011$), such that the difference in head sway NPL between stationary and optic flow stimulation periods was 52% larger in individuals with VV than in CON (Fig. 3). This finding suggests that optic flow affected the balance of the VV group to a greater degree than the CON group. In fact, post-hoc testing revealed that during the stationary period, the groups differed by 0.37 cm/s ($p = .08$), whereas during the optic flow period, the difference between groups was 0.79 cm/s ($p = .02$). Conversely, there was not a significant interaction between group and condition (platform and optic flow frequency), indicating that group responses to the different conditions followed the same pattern. ($F_{(3,41.4)} = 1.23$, $p = .311$). Finally, there was a significant interaction between test condition and visual stimulation period ($F_{(3,84.8)} = 11.99$, $p < .001$) (Fig. 4). The difference in head sway NPL going from the stationary field to optic flow when standing on a sway-referenced platform was approximately 165%

Table 1

Diagnoses, gender, and vestibular test results of fifteen individuals with visual vertigo. Videonystagmography oculomotor screening was normal for all subjects.

Diagnoses	Gender	Positional	Caloric	Rotational	VEMP
Vestibular migraine	Female	Normal	25% right reduction	Normal	N/A
Dizziness of uncertain etiology	Female	Normal	Normal	Normal	Normal
Vestibular migraine	Female	Normal	Normal	Normal	N/A
Dizziness of uncertain etiology	Female	Normal	Normal	Normal	Bilaterally decreased
Meniere's disease (uncertain laterality)	Male	Normal	43% left reduction	Right DP	Bilaterally decreased, worse on the right
Dizziness of uncertain etiology	Female	Normal	Normal	Normal	Normal
Migraine-anxiety-related dizziness	Female	Direction fixed	37% right reduction	Left DP	N/A
Dizziness of uncertain etiology	Male	Normal	N/A	Left DP	Normal
Post-concussion dizziness	Female	Normal	N/A	Normal	Normal
Right Meniere's disease	Male	Normal	Absent right (ice)	Left DP	N/A
Post-traumatic benign paroxysmal positional vertigo variant	Female	Normal	Normal	Normal	Left decreased
Persistent postural-perceptual dizziness	Female	Normal	Normal	Normal	Normal
Vestibular migraine with unilateral vestibular loss	Female	Normal	47% right reduction	Normal	Normal
Post-traumatic right peripheral vestibulopathy	Female	Normal	Normal	Normal	Right decreased
Right unilateral vestibular loss	Male	Direction fixed	25% right reduction	Normal	Normal

DP, directional preponderance; VEMP, cervical vestibular evoked myogenic potential.

Table 2

Change in cerebral activation (oxyhemoglobin concentration) when viewing single sine optic flow and standing on a fixed surface in individuals with visual vertigo (VV) and healthy controls (CON).

Group	Region of interest	Beta	SE	t	p	q
VV	Left middle frontal	−0.88	0.50	−1.77	0.08	0.16
	Left superior temporal	1.08	0.70	1.53	0.13	0.23
	Left occipital	1.13	0.58	1.94	0.05	0.13
	Right middle frontal	−0.91	0.47	−1.93	0.05	0.13
	Right superior temporal	−0.20	0.71	−0.28	0.78	0.87
	Right occipital	0.39	0.55	0.71	0.48	0.66
CON	Left middle frontal	1.65	0.40	4.11	< 0.001	< 0.001*
	Left superior temporal	0.19	0.80	0.23	0.82	0.87
	Left occipital	0.99	0.52	1.92	0.06	0.13
	Right middle frontal	2.53	0.58	4.35	< 0.001	< 0.001*
	Right superior temporal	0.26	0.68	0.38	0.71	0.85
	Right occipital	1.37	0.65	2.10	0.04	0.13
VV - CON	Left middle frontal	−2.53	0.64	−3.95	< 0.001	< 0.001*
	Left superior temporal	0.89	1.06	0.84	0.40	0.60
	Left occipital	0.14	0.78	0.17	0.87	0.87
	Right middle frontal	−3.45	0.75	−4.59	< 0.001	< 0.001*
	Right superior temporal	−0.46	0.98	−0.46	0.64	0.83
	Right occipital	−0.98	0.86	−1.15	0.25	0.41

Beta = regression coefficients; SE = standard error; t = t-statistic; p = p-value; q = q-value.

* Indicates $p \leq .05$, false discovery rate-corrected.

larger than when standing on a fixed platform.

4. Discussion

In this study, fNIRS was used to investigate cerebral activation in individuals with VV and CON during optic flow. The primary finding was decreased activation in the bilateral middle frontal regions of the VV group when viewing optic flow on a fixed platform in comparison to the CON. Suppressed activation was also seen in the right middle frontal region in the VV group when viewing sum of sines optic flow on a sway-referenced platform in comparison to the CON.

During the fixed platform conditions, both VV and CON had increased activation in the superior temporal and occipital regions of interest during optic flow stimulation relative to the stationary visual scene. During the single sine condition, the changes did not reach the level of statistical significance, suggesting that the predictable optic

Table 3

Change in cerebral activation (oxyhemoglobin concentration) when viewing sum of sines optic flow and standing on a fixed surface in individuals with visual vertigo (VV) and healthy controls (CON).

Group	Region of interest	Beta	SE	t	p	q
VV	Left middle frontal	−1.55	0.54	−2.89	0.005	0.014*
	Left superior temporal	2.78	0.86	3.24	0.002	0.009*
	Left occipital	1.01	0.58	1.74	0.08	0.15
	Right middle frontal	−0.68	0.54	−1.26	0.21	0.29
	Right superior temporal	0.87	0.77	1.14	0.26	0.33
	Right occipital	1.35	0.58	2.32	0.02	0.045*
CON	Left middle frontal	0.96	0.41	2.32	0.02	0.045*
	Left superior temporal	1.03	0.76	1.35	0.18	0.27
	Left occipital	1.20	0.51	2.35	0.02	0.045*
	Right middle frontal	1.66	0.51	3.25	0.002	0.009*
	Right superior temporal	0.73	0.67	1.08	0.28	0.34
	Right occipital	1.79	0.58	3.08	0.003	0.01*
VV - CON	Left middle frontal	−2.51	0.68	−3.71	< 0.001	0.006*
	Left superior temporal	1.75	1.15	1.53	0.13	0.21
	Left occipital	−0.18	0.78	−0.24	0.81	0.86
	Right middle frontal	−2.34	0.74	−3.16	0.002	0.009*
	Right superior temporal	0.14	1.02	0.14	0.89	0.89
	Right occipital	−0.43	0.82	−0.53	0.60	0.67

Beta = regression coefficients; SE = standard error; t = t-statistic; p = p-value; q = q-value.

* Indicates $p \leq .05$, false discovery rate-corrected.

flow movement did not elicit sustained activity in the occipital visual processing areas, and furthermore, did not require additional vestibular related activity in the superior temporal region to stabilize posture. During the sum of sines optic flow condition, significantly increased activity was observed in the bilateral occipital regions for CON and the right occipital region in VV, indicating that the unpredictable optic flow stimulation required a greater degree of visual processing compared with the single sine optic flow. It is interesting that this condition also produced significantly greater activation in the left superior temporal region of VV, but not CON, which could be interpreted as the VV needing greater vestibular involvement to maintain balance, which was confirmed by the postural sway results. In previous studies using fNIRS, bilateral activation of the superior temporal and supramarginal gyri 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 et al., 2017; Takakura et al., 2015). These brain regions are important for multi-sensory integration. In this study, visual information was present, but the optic flow was in conflict with other sensory cues for postural orientation.

The biggest difference in activation between VV and CON during the

Table 4
Change in cerebral activation (oxyhemoglobin concentration) when viewing single sine optic flow and standing on a sway-referenced surface in individuals with visual vertigo (VV) and healthy controls (CON).

Group	Region of interest	Beta	SE	t	p	q
VV	Left middle frontal	2.24	0.49	4.05	< 0.001	< 0.001*
	Left superior temporal	3.85	0.84	4.60	< 0.001	< 0.001*
	Left occipital	1.41	0.60	2.36	0.020	0.033*
	Right middle frontal	0.92	0.53	1.72	0.09	0.12
	Right superior temporal	5.14	0.69	7.42	< 0.001	< 0.001*
	Right occipital	1.30	0.54	2.40	0.018	0.033*
CON	Left middle frontal	1.92	0.42	4.53	< 0.001	< 0.001*
	Left superior temporal	2.21	0.71	3.11	0.002	0.005*
	Left occipital	1.72	0.54	3.21	0.002	0.005*
	Right middle frontal	2.32	0.55	4.25	< 0.001	< 0.001*
	Right superior temporal	4.79	0.72	6.64	< 0.001	< 0.001*
	Right occipital	1.62	0.68	2.38	0.019	0.033*
VV - CON	Left middle frontal	0.32	0.65	0.49	0.63	0.73
	Left superior temporal	1.64	1.10	1.49	0.14	0.18
	Left occipital	−0.31	0.80	−0.39	0.70	0.73
	Right middle frontal	−1.40	0.76	−1.83	0.07	0.11
	Right superior temporal	0.35	1.00	0.35	0.73	0.73
	Right occipital	−0.32	0.87	−0.37	0.71	0.73

Beta = regression coefficients; SE = standard error; *t* = *t*-statistic; *p* = *p*-value; *q* = *q*-value.
  * Indicates *p* ≤ .05, false discovery rate-corrected.

Table 5
Change in cerebral activation (oxyhemoglobin concentration) when viewing sum of sines optic flow and standing on a sway-referenced surface in individuals with visual vertigo (VV) and healthy controls (CON).

Group	Region of interest	Beta	SE	t	p	q
VV	Left middle frontal	1.99	0.48	4.16	< 0.001	< 0.001*
	Left superior temporal	2.95	0.75	3.96	< 0.001	< 0.001*
	Left occipital	0.58	0.57	1.01	0.31	0.35
	Right middle frontal	1.85	0.49	3.74	< 0.001	< 0.001*
	Right superior temporal	3.77	0.71	5.28	< 0.001	< 0.001*
	Right occipital	2.38	0.61	3.87	< 0.001	< 0.001*
CON	Left middle frontal	3.31	0.41	8.04	< 0.001	< 0.001*
	Left superior temporal	2.07	0.72	2.88	0.005	0.007*
	Left occipital	1.63	0.51	3.19	0.002	0.003*
	Right middle frontal	4.96	0.58	8.61	< 0.001	< 0.001*
	Right superior temporal	5.81	0.71	8.20	< 0.001	< 0.001*
	Right occipital	2.14	0.57	3.77	< 0.001	< 0.001*
VV - CON	Left middle frontal	−1.32	0.63	−2.09	0.039	0.054
	Left superior temporal	0.88	1.03	0.86	0.39	0.41
	Left occipital	−1.05	0.77	−1.36	0.18	0.21
	Right middle frontal	−3.11	0.76	−4.10	< 0.001	< 0.001*
	Right superior temporal	−2.04	1.01	−2.02	0.046	0.059
	Right occipital	0.23	0.84	0.28	0.78	0.78

Beta = regression coefficients; SE = standard error; *t* = *t*-statistic; *p* = *p*-value; *q* = *q*-value.
  * Indicates *p* ≤ .05, false discovery rate-corrected.

fixed platform conditions occurred in the middle frontal regions. When viewing single sine or sum of sines optic flow while standing on a fixed platform, the VV group displayed reduced activation in the middle frontal regions compared with the stationary baseline periods, as indicated by the negative regression coefficients, although it was only

significant in the left middle frontal region during sum of sines optic flow. Coupled with the significant increase in activation for the CON, a group difference in the response to optic flow was evident.

The middle frontal region has been documented as an active region during vestibular stimulation in many studies (Lopez and Blanke, 2011), including caloric stimulation (Dieterich et al., 2003b), auditory-evoked vestibular stimulation (Van Ombergen et al., 2017; Miyamoto et al., 2007), and galvanic vestibular stimulation (Bense et al., 2001; Stephan et al., 2005; Della-Justina et al., 2015; Lobel et al., 1998). The activation of this region has been attributed to its role in performing oculomotor and fixation tasks (Bense et al., 2001; Sweeney et al., 1996), and its connections to both visual association areas[4] and spatial navigation and memory areas (Cha et al., 2012).

There are several reports of middle frontal gyrus abnormalities in clinical vestibular syndromes. For example, Cha et al. (Cha et al., 2012) observed decreased glucose metabolism and decreased resting state connectivity in the middle frontal gyrus in individuals with persistent mal de debarquement (Cha et al., 2012). Furthermore, in patients with mal de debarquement, a longer duration of symptoms was related to reduced volume in the left middle frontal gyrus (Cha and Chakrapani, 2015). In people with bilateral vestibular hypofunction, a weaker resting state connectivity between the posterior insula and middle frontal gyrus was found (Göttlich et al., 2014). This is similar to the results of Indovina et al. who found that patients with chronic subjective dizziness showed lesser activation in the bordering inferior frontal gyrus and superior temporal gyrus in comparison to healthy controls in response to sound-evoked vestibular stimuli using fMRI (Indovina et al., 2015). Indovina et al. also found reduced connectivity between the left inferior frontal gyrus and right superior temporal gyrus in individuals with chronic subjective dizziness compared with controls, and suggested that prefrontal (i.e., middle and inferior frontal) control over the normal inhibitory interactions between the visual and vestibular areas may be modified by chronic visual dependence (Indovina et al., 2015).

Consequently, our data suggest that individuals with vestibular disorders who have high levels of visual vertigo have reduced activation patterns in the middle frontal gyrus that are similar to people who have bilateral vestibular hypofunction, mal de debarquement, or chronic subjective dizziness. Most of the VV had some type of central and/or peripheral vestibular disorder resulting in dizziness. In an attempt to limit dizziness due to visual-vestibular conflict, the decreased middle frontal activation could indicate decreased weighting of vestibular information. It is important to note, however, that one group has reported contrary findings of increased connectivity between visual association areas and middle frontal gyrus in people with visually induced dizziness (Van Ombergen et al., 2017). If this is the case, then greater visual stimulation could produce reduced activation in the middle frontal gyrus through normal reciprocal inhibition (Brandt et al., 1998, 2002; Bense et al., 2004).

When viewing optic flow while standing on a sway-referenced platform, large increases in activation in most regions occurred for both VV and CON. The increase in the occipital and superior temporal regions occurred as the sway-referenced platform condition reduced accurate somatosensory input and thus increased weighting of visual and vestibular cues needed for balance. Both groups also demonstrated an increase in middle frontal activation, which can be attributed to the greater vestibular stimulation with increased body sway (Van Ombergen et al., 2017; Bense et al., 2001; Stephan et al., 2005; Della-Justina et al., 2015; Dieterich et al., 2003b; Miyamoto et al., 2007; Lobel et al., 1998), or increased reliance on visual cues due to the reduction in somatosensory input (Van Ombergen et al., 2017). During the single sine optic flow condition, there was no significant difference in activation in any region between the VV and CON. On the contrary, during sum of sines optic flow, VV once again demonstrated relative reduction in the middle frontal regions compared with CON. Thus, it is possible that the predictability of the optic flow stimuli plays a role in
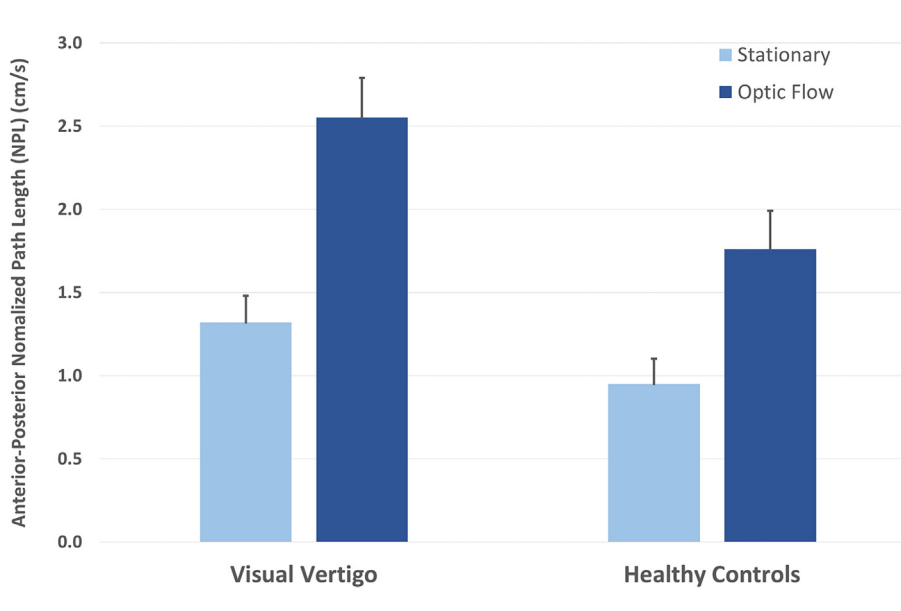
Fig. 3. Anterior-posterior (AP) head sway normalized path length (NPL) between stationary and optic flow periods for patients with visual vertigo and healthy controls. Error bars represent standard error.

prefrontal control of posture.

Other studies have investigated imaging of cortical areas in individuals with VV. During resting state fMRI, patients with visually induced dizziness had decreased functional connectivity in the right superior temporal gyrus, and increased connectivity in the precuneus and middle frontal gyrus (Van Ombergen et al., 2017). In their small sample of ten patients, nine out of ten 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). 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 platform 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 cerebral activation 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 cerebral activation were seen in the subjects with VV in this study.

Postural sway was greater in VV than in CON, as measured by NPL of the head in the AP direction. Patients with vestibular disorders (Guerraz et al., 2001; Redfern and Furman, 1994), migraine-related dizziness (Furman et al., 2005), visual vertigo (Bronstein, 1995; Guerraz et al., 2001; Keshner et al., 2007; Pavlou et al., 2006), visual-vestibular mismatch (Van Ombergen et al., 2016), visual sensitivity (Keshner and Dhaher, 2008), phobic postural vertigo (Krafczyk et al., 1999), and space and motion discomfort[54] have also displayed greater
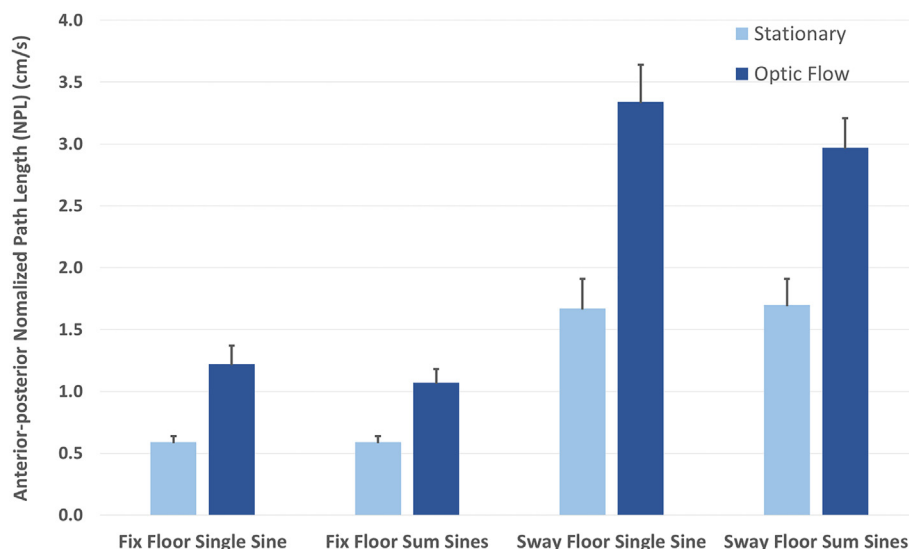

Fig. 4. Anterior-posterior head sway normalized path length (NPL) during stationary (light blue) and optic flow (dark blue) visual stimulation periods during four testing conditions. Error bars represent standard error. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

sway than healthy controls during conditions of varying visual input (such as optic flow and eye closure). Unlike Jacob et al. (Jacob et al., 1995), persistence of increased postural sway after optic flow periods was not observed in this study.

The lesser sway observed during sum of sines optic flow in comparison to single sine optic flow while standing on a sway-referenced platform in this study is consistent with the results of Musolino et al. (Musolino et al., 2006) who used similar visual stimuli. 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).

This is the first study to apply functional brain imaging during a standing balance task in individuals with VV in comparison to healthy adults. The VV had a variety of central and/or peripheral vestibular disorders, typical of those referred for vestibular physical therapy. Due to the small size and heterogeneity of the VV group, only preliminary conclusions about the neural basis of VV can be drawn from this study. Future studies could refine this approach by using a larger sample size and by only including individuals with similar diagnoses.

The use of fNIRS provided a means to record changes in cerebral activation while the subjects performed a standing balance task. However, limited areas were imaged with fNIRS due to the head cap design and depth of penetration. Future studies may benefit from a multimodal imaging approach that would combine fNIRS and fMRI to better understand the spatiotemporal dynamics of the hemodynamic response to optic flow with high spatiotemporal resolution (Yuan and Ye, 2013). Specific task-based assessment of the hemodynamic response in individuals with VV employing visual, vestibular, or a combination of visual and vestibular stimulation may elucidate our fundamental understanding of the neural basis of VV. It is not known if lesser activity in the middle frontal region during optic flow in individuals with VV is a physiological impairment or a coping mechanism. Future studies should explore if this decreased activation is modified following a rehabilitation regimen consisting of visual habituation exercises.

5. Conclusions

fNIRS was used to record changes in cerebral activation in individuals with VV and CON while they viewed AP optic flow. Cerebral activation was decreased in VV in comparison to CON in the bilateral middle frontal regions when single and sum of sines optic flow was viewed while standing on a fixed platform. Cerebral activation was also decreased in the right middle frontal region when sum of sines optic flow was viewed while standing on a sway-referenced platform. Although preliminary, these findings add to a growing body of literature using functional brain imaging to explore changes in cerebral activation in individuals with complaints of dizziness, disorientation, and unsteadiness. Future work could extend these preliminary findings by applying multimodal neuroimaging methods to larger samples of individuals with VV. Specific task-based assessments during combined fNIRS and fMRI may further our fundamental understanding of the neural basis of VV. The therapeutic implications of these findings should be explored to determine if this same cerebral activation pattern can be modified with physical therapy intervention, such as habituation exercises using optic flow.

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Conflicts of interest

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