THE INTERSECTION BETWEEN VESTIBULAR FUNCTION AND SPATIAL MEMORY IN ADULTS WITH CHRONIC MODERATE-SEVERE TRAUMATIC BRAIN INJURY

By

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This dissertation is dedicated to the memory of my late grandfather, Gerald Feller.

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CHAPTER 1

Background

1.1 Introduction

Traumatic Brain Injury (TBI) is a leading cause of death and disability with more than 1.5 million people sustaining a TBI each year in the United States (V. Y. Ma, Chan, & Carruthers, 2014) and an estimated 50-60 million new TBI cases annually worldwide (Maas et al., 2017). Vestibular symptoms, such as dizziness and/or vertigo, are among the most reported complaints from patients with TBI (Maskell, Chiarelli, & Isles, 2006). However, there are limited prospective studies assessing vestibular symptoms in adults with chronic moderate-severe TBI and currently no hypothesis-driven studies that examine peripheral vestibular function in this population. Furthermore, several lines of evidence show anatomical connections between the vestibular system and brain areas involved in spatial cognition (e.g., hippocampus; for review, see Bigelow & Agrawal, 2015; Ferrè & Haggard, 2020; Hitier, Besnard, & Smith, 2014; Smith, 1997, 2017), and both TBI and vestibular damage can cause hippocampal atrophy and spatial cognitive impairment. However, it is unclear what influence vestibular impairments have on spatial cognitive deficits commonly observed in adults with TBI. The aim of this dissertation was threefold: to assess the 1) prevalence of vestibular symptoms, 2) prevalence of peripheral vestibular impairment, and 3) correlation between peripheral vestibular function and spatial cognition, in adults with chronic moderate-severe TBI. Overall, understanding the vestibular symptomatology and the frequency and location of peripheral vestibular impairment in adults with chronic moderate-severe TBI can lead to more appropriate triage, evidence-based decisions about test batteries, and comprehensive rehabilitation programs for this TBI population (Šarkić et al., 2021). Additionally, understanding the relationship between peripheral vestibular function and spatial cognition may have further implications for treatment and rehabilitation plans for patients with vestibular and/or primary neurological disorders, such as TBI.

1.2 The Vestibular System

1.2.1 The peripheral vestibular system consists of five inner ear organs.

The vestibular system is a sensory system responsible for detecting head motion to maintain postural control and gaze stability. The peripheral vestibular system consists of five sensory organs in the inner ear that make up the vestibular labyrinth: two otolith organs, the utricle and saccule, and three semicircular canals (SCCs), the anterior, posterior, and horizontal. Each peripheral vestibular organ contains neural receptors that project information to the brain about head acceleration and rotation, with the combined information of all five organs representing head motion in three dimensions. The SCCs are responsible for projecting information about angular head rotations, while the otolith organs are responsible for projecting information about linear acceleration (Jacobson & Shepard, 2016).

1.2.2 The vestibular system controls three vestibular reflexes.

The five organs of the peripheral vestibular system send neural signals via the vestibular nerve to the central vestibular system, which controls a series of vestibular reflexes. The primary role of the vestibuo-ocular reflex (VOR) is to maintain eye stability during head movements. The vestibulospinal reflex (VSR) is responsible for maintaining an individual's posture and center of mass. The purpose of the vestibulocolic reflex (VCR) is to maintain head stability during body movements. The SCCs are involved in VOR and VSR activity (Hain & Cherchi, 2014), whereas the otolith organs mediate the VOR (utricle), VSR (saccule), and VCR (saccule) (Jacobson & Shepard, 2016).

Several brain structures, nerves, and muscles are involved in the VOR, VSR, and VCR. The VOR pathway involves structures such as the vestibular, abducens, and oculomotor nerves, the vestibular, abducens, and oculomotor nuclei, and the lateral and medial rectus muscles of the eyes (Somisetty & Das, 2024). The VSR pathway includes the vestibular nerve and nuclei, the lateral and medical vestibulospinal tracts, the reticulospinal tract, and numerous muscles of the body, including those of the arms and legs

(Jacobson & Shepard, 2016). The VCR pathway involves the vestibular nerve and nuclei and multiple muscles of the neck, including the sternocleidomastoid (SCM) muscle (Jacobson & Shepard, 2016). Importantly, all three vestibular reflexes driven by otolith organs involve muscle activity that can be measured using electromyography (EMG).

1.2.3 The vestibular system has anatomical connections to brain regions involved in memory.

Several lines of evidence show that vestibular structures, such as the vestibular nuclei, project to brain regions involved in memory, such as the hippocampus (for review, see Hitier et al., 2014; Smith, 1997). These anatomical connections occur mainly via the thalamus in at least four major neural pathways (for review, see Hitier et al., 2014; Smith, 1997). It is well-established that the hippocampus plays a major role in spatial cognitive abilities, such as spatial relational memory (Crane & Milner, 2005; Hannula, Tranel, & Cohen, 2006) and navigation and environmental exploration (Maguire, Nannery, & Spiers, 2006; Voss, Gonsalves, Federmeier, Tranel, & Cohen, 2011; Voss, Warren, et al., 2011; Yee et al., 2014). However, the hippocampus may also be involved in "vestibular memory" (Wiest et al., 1996), although this research area is underexplored.

1.3 Traumatic Brain Injury (TBI)

1.3.1 TBI is a significant public health concern.

Traumatic Brain Injury (TBI) often results in chronic lifelong disability, placing a huge economic burden on individuals, families, and society (Maas et al., 2022). TBI affects at least 1.74 million people per year in the United States, and up to 5.4 million people are affected by long-term disability following TBI (V. Y. Ma et al., 2014). Worldwide, there are an estimated 50-60 million new TBI cases annually (Maas et al., 2017). Furthermore, TBI costs approximately $81 million USD in direct healthcare costs and up to $2.3 billion USD in indirect healthcare costs; indirect non-healthcare costs, such as productivity loss, are estimated to be $1.1 billion USD annually (Humphreys, Wood, Phillips, & Macey, 2013). It is

estimated that following appropriate treatment guidelines for patients with TBI can lead to substantial patient medical savings of approximately $11,000 USD and societal savings totaling more than $3 billion USD (Faul, Rutland-Brown, Frankel, Sullivent, & Sattin, 2007). Thus, improving assessment and treatment of TBI-related symptoms is imperative to improve survivors' quality of life and lessen the economic impact of injury-related disability.

1.3.2 TBI is characterized by injury severity and phase.

TBI is often classified by injury severity and phase. TBI severity ranges from mild to severe based on Glasgow Coma Scale (GCS) score, duration of post-traumatic amnesia (PTA), duration of loss of consciousness (LOC), and neuroimaging findings (Malec et al., 2007). TBI phase is defined as acute or chronic based on the time since injury (Salmond, Menon, Chatfield, Pickard, & Sahakian, 2006). A duration of six months post-injury is a conservative cutoff often used to define the chronic stage (Duff et al., 2022), although there is variation among clinicians and researchers concerning the distinction between acute and chronic phases.

1.3.3 TBI is associated with symptoms that may be vestibular in origin.

TBI results in various symptomologies depending on the location and extent of brain injury. However, symptoms that may be vestibular in origin, such as dizziness and/or vertigo, are among the most reported complaints among patients with TBI (Maskell et al., 2006). For example, between 23% and 81% of patients with mild or moderate TBI in the acute phase (<6 months post injury) reported dizziness and/or vertigo (Maskell et al., 2006). At least five years post injury (chronic phase), 20-32% patients with mild TBI and 37-47% of patients with moderate TBI reported dizziness and/or vertigo symptoms (Maskell et al., 2006). Furthermore, adverse effects associated with vestibular dysfunction are likely to be more severe in patients with TBI due to comorbidity with other disorders (Chan, Mollayeva, Ottenbacher, & Colantonio, 2017).

1.3.4 TBI is associated with damage to the vestibular system.

Several areas along the vestibular pathway can be damaged following TBI, including the semicircular canals and otolith organs of the inner ear, which can lead to dizziness and balance problems (for review, see Šarkić et al., 2021). For example, a retrospective study of non-blast related acute mild TBI by Basta et. al. showed that up to 65% of participants with TBI had otolith dysfunction (Basta, Todt, Scherer, Clarke, & Ernst, 2005). A second study by the same research group showed that 5-7% of participants with TBI had evidence of semicircular canal dysfunction following injury (Ernst et al., 2005). However, a comprehensive review of the literature revealed a substantial scarcity of prospective studies examining peripheral vestibular function following TBI and an even further paucity of experiments designed to assess vestibular function in TBI populations using standard vestibular audiology clinical methods (Šarkić et al., 2021). Furthermore, there are currently no published hypothesis-driven, prospective studies investigating peripheral vestibular function in adults with chronic moderate-severe TBI. This proposal aims to contribute to the limited available literature in this area. There has recently been a call for a new approach to TBI classification based on multimodal quantifiable measures (Tenovuo et al., 2021), and the addition of vestibular testing in the clinical diagnosis of TBI could provide further quantifiable data. Ultimately, understanding the frequency, type, and location of vestibular deficits in patients with TBI can lead to more appropriate triage, evidence-based decisions about test batteries, and comprehensive rehabilitation programs for the TBI patient population (Šarkić et al., 2021).

1.3.5 TBI and vestibular impairment are associated with hippocampal atrophy and impaired spatial cognition.

TBI is associated with diffuse neuropathology affecting cortical and subcortical areas, along with the connecting white matter tracks, which can cause a series of cognitive symptoms post-injury (for review, see Covington & Duff, 2021). As such, TBI can result in spatial cognitive impairments, such as spatial reconstruction deficits (Rigon, Schwarb, Klooster, Cohen, & Duff, 2020), as well as impairments

in navigation and environmental exploration (J.M. et al., 1997; Lehnung et al., 2001; Skelton, Bukach, Laurance, Thomas, & Jacobs, 2000; Skelton, Ross, Nerad, & Livingstone, 2006; Sorita et al., 2013). Recent studies have also suggested vestibular loss is associated with deficits in spatial memory, navigation, and hippocampal atrophy (Brandt et al., 2005). For example, Brandt et. al. showed that patients with chronic bilateral vestibular loss took significantly more time and significantly longer paths to navigate a virtual water maze compared to control participants (Brandt et al., 2005). This suggests vestibular function may be critical for spatial memory and is unsurprising given the anatomical connections between the vestibular system and brain areas involved in spatial cognition (e.g., hippocampus).

Importantly, both TBI and vestibular damage are associated with hippocampal atrophy (Bigler, 2021; Brandt et al., 2005). Several studies have confirmed hippocampal damage, including decreased hippocampal volumes, in patients with TBI (for review, see Bigler, 2021), and especially in those with moderate-severe TBI (for review, see Harris, de Rooij, & Kuhl, 2019). Additionally, one study showed that patients with vestibular loss, but no known neurological deficits, had decreased hippocampal volumes, and that their spatial memory impairments that matched their pattern of hippocampal atrophy (Brandt et al., 2005). However, it is unknown what influence peripheral vestibular impairments have on spatial cognitive deficits commonly observed in adults with TBI.

CHAPTER 2

Vestibular Symptoms in Adults with Chronic Moderate-Severe TBI*

*This chapter is adapted from the following research article: Romero, D. J., Feller, J., Clough, S., Jacobson, G., Roberts, R. A., & Duff, M. (2024). Self-Reported Symptoms of Vertigo and Imbalance Are Prevalent Among Adults with Chronic Moderate–Severe Traumatic Brain Injury: A Preliminary Analysis. *American journal of audiology*, *33*(1), 269-274. DOI: 10.1044/2023_AJA-23-00100.

2.1 Introduction

Traumatic brain injury (TBI) is a significant public health concern and the leading cause of death and disability among adults in the United States. In the United States alone, TBI impacts approximately 1.5 million people, with 230,000 hospitalizations each year. TBI also has significant economic consequences, costing approximately $81 million in direct health care costs and up to $2.3 billion in indirect health care costs; indirect non–health care costs, such as productivity loss, are estimated to be $1.1 billion annually (Humphreys et al., 2013). TBI is associated with diffuse neuropathology affecting cortical and subcortical areas, and the connecting white matter tracks, and significant heterogeneity in the presence and severity of physical and cognitive symptoms postinjury (see Covington & Duff, 2021, for a review). During the acute phase of injury, dizziness and imbalance are among the most commonly reported injury consequences (Kleffelgaard et al., 2017; Maskell et al., 2006). These symptoms are not surprising given the vulnerability and complexity of subcortical and cortical structures involved in vestibular reflexes. While it is known that dizziness and imbalance occur during the acute phase of injury (i.e., less than 6 months), less is known about the presence of these symptoms within the chronic phase of injury (i.e., greater than 6 months). Available evidence suggests that dizziness and imbalance can persist

well into the chronic phase (Maskell et al., 2006). However, descriptions of the frequency and type of symptoms are limited in this population. In this research note, our aim was to prospectively characterize symptoms of dizziness and imbalance in a sample of adults with chronic moderate–severe TBI.

2.2 Methods

2.2.1 Participants

This study protocol was approved by the institutional review board (IRB #221051) at Vanderbilt University Medical Center (VUMC). In this research note, we present preliminary data from 43 participants, 24 adults with chronic moderate–severe TBI and 19 noninjured comparison (NC) participants. Participants were recruited from the Vanderbilt Brain Injury Patient Registry at VUMC. Individuals with and without a history of TBI were invited to participate in a brain injury registry using a variety of methods (institutional mass e-mail, social media, flyers, word of mouth, mailers). For more detailed information about the registry, see Duff et al. (2022). Participants who enrolled in the TBI group were between 18 and 55 years of age to limit the effects of developmental changes as well as age-related cognitive and vestibular decline (Iwasaki & Yamasoba, 2015; Salthouse, 2009). Each participant with TBI sustained a single moderate– severe TBI, as determined using the Mayo Classification System (Malec et al., 2007), and met at least one of the following criteria: (a) Glasgow Coma Scale < 13 within the first 24 hr of acute care admission, (b) positive neuro imaging finding (acute computed tomography findings or lesions visible on magnetic resonance imaging during the chronic phase of injury), (c) loss of consciousness (LOC) > 30 min, and (d) posttraumatic amnesia > 24 hr. This information was obtained from available medical records and a semistructured participant interview. The semistructured interview asked participants about the circumstances (e.g., car accident, fall) and characteristics (e.g., retrograde amnesia) of the brain injury. These details were verified, to the extent possible, with available medical records. The semistructured interview also asked about changes to various cognitive systems since the onset of their brain injury that interfere with daily function including memory, attention and

concentration, speech and language, motor, personality, and executive functions (e.g., “Since your injury, have you experienced changes in your memory? This could be changes in remembering things from the past or learning new things.”). Finally, we obtained information about their academic, vocational, and interpersonal history. The interview was conducted one-on-one with participants by our Clinical and Translational Research Coordinator and was completed in approximately 30 min. Interviews were conducted either in person or via teleconference (e.g., Zoom). Participants with TBI were in the chronic phase of injury (> 6 months postinjury). Thus, participants’ neuropsychological profiles were stable (Salmond et al., 2006). A group of NC participants with no history of neurological or cognitive disability, hearing loss, or dizziness and imbalance was also enrolled into the study protocol. Participant groups were demographically matched on sex, age (± 5 years), and education (± 2 years). The majority of participants with TBI were female (54%) with a mean age of 38 years (SD = ± 10 years). The average time since their TBI was 6 years (SD = ± 6 years). The group of NC participants (58% female) had a mean age of 38 years (SD = ± 9 years). Table 2.1 shows demographic information of the TBI group.

TABLE 2.1. Demographic and injury information for each participant with TBI.

Participant	Sex	Age (years)	EDU	TSO	GCS	Etiology	LOC	PTA	Neuroimaging
1	F	21-25	12	13	14	MVA	N/A	> 24 hrs	SAH
2	F	36-40	16	77	3	MVA	> 30 min	> 24 hrs	SAH
3	F	21-25	12	61	13	MVA	> 30 min	> 24 hrs	SAH
4	F	51-55	12	29	15	Ground-level fall	No LOC	No PTA	SAH, SDH
5	M	31-35	18	57	15	Ground-level fall	> 30 min	< 24 hrs	SAH, IPH
6	F	31-35	16	18	15	MVA	< 30 min	N/A	SAH
7	M	31-35	12	14	7	MVA	> 30 min	> 24 hrs	SAH
8	M	41-45	12	69	3	Other	> 30 min	> 24 hrs	ICH, PCH, SAH, SDH
9	F	41-45	18	74	3	MVA	> 30 min	> 24 hrs	EDH, SAH
10	M	26-30	16	24	3	Ped vs. auto	> 30 min	> 24 hrs	EDH, SAH, SDH
11	F	31-35	16	98	10	MVA	No LOC	> 24 hrs	No acute intracranial findings
12	M	26-30	12	8	7	MCC	> 30 min	> 24 hrs	Shear/DAI
13	F	46-50	16	75	6	Ped vs. auto	N/A	> 24 hrs	SAH, SDH
14	M	26-30	12	13	15	Ped vs. auto	No LOC	< 24 hrs	IPH, SAH, SDH, hemorrhagic contusions
15	F	41-45	12	117	3	MVA	> 30 min	> 24 hrs	SAH, SDH, uncal herniation
16	M	36-40	20	49	15	Struck by object	< 30 min	< 24 hrs	SDH, scattered SAH, right temporal hemorrhage
17	F	31-35	14	50	9	MVA	< 30 min	> 24 hrs	SAH, SDH
18	M	51-55	12	276	N/A	MVA	> 30 min	> 24 hrs	Hemorrhage
19	F	51-55	16	50	14	MVA	< 30 min	< 24 hrs	SAH, SDH
20	F	36-40	16	250	N/A	MVA	> 30 min	> 24 hrs	SAH, possible right frontal contusion
21	M	51-55	16	237	N/A	MVA	> 30 min	> 24 hrs	N/A
22	F	46-50	16	72	9	MVA	< 30 min	> 24 hrs	SDH, PCH, arachnoid hemorrhage
23	M	46-50	16	25	3	Fall from height	> 30 min	> 24 hrs	SAH
24	M	21-25	12	10	3	MVA	> 30 min	> 24 hrs	ICH, IVH, PCH, SAH, SDH, DAI

Note: Education (EDU) reflects years of highest degree obtained; MCC includes both motorcycle and snowmobile accidents; Time since injury onset (TSO) is presented in months; Loss of consciousness (LOC) is presented in minutes; Glasgow Coma Scale (GCS) is total score at the time of first postinjury measurement; PTA = posttraumatic amnesia; MVA = motor vehicle accident; N/A = information was not available; SAH = subarachnoid hemorrhage; Ped vs. auto = participant was hit by a car while walking or running; SDH = subdural hematoma; EDH = epidural hematoma; PCH = parenchymal hemorrhage; IPH = intraparenchymal hemorrhage; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; DAI = diffuse axonal injury.

2.2.2 Measurement

We administered a modified version of a standard case history form (Furman & Cass, 1996) to all participants. This case history form allowed the participant to denote the presence, type, and description of any dizziness and imbalance concerns. All patients answered “yes” or “no” to a series of questions

about whether they experience dizziness (consisting of vertigo and nonvertigo symptoms), imbalance, and related symptoms. Participants were asked only to endorse active symptoms.

2.2.3 Statistical analysis

Fisher's exact test (Fisher, 1970) was used to deter mine whether there was a significant association between group (TBI or NC) and self-reports of dizziness, imbalance, and related symptoms ("yes" or "no"). Additionally, this test was used to identify any significant associations among self-reported symptoms (e.g., dizziness and imbalance, hearing loss, head pressure, emesis, nausea, headache, and LOC). For example, we aimed to determine whether someone who endorsed "yes" on one question was significantly more likely to answer "yes" on another question. Specifically, given the close association between vertigo, imbalance, and headache symptoms in common vestibular disorders (e.g., vestibular migraine), we were interested in determining whether there were any significant associations between these symptoms in participants with chronic moderate–severe TBI. The alpha was set to $p < .05$ for all tests.

2.3 Results

2.3.1 Frequency of dizziness and imbalance

An independent-samples t test revealed that the TBI and NC groups were not significantly different on age ($p = 0.834$), sex ($p = 0.812$), or education level ($p = 0.902$). The frequency of each reported symptom for both groups is displayed as a percentage of those endorsing each question (i.e., "yes"), which can be found in Figure 2.1. Figure 2.1 displays the frequency of symptoms reported by both the TBI and NC groups. Dizziness was reported by 83% (20/24) of the participants within the TBI group. Within the category of dizziness, 75% (18/24) of the TBI group reported lightheadedness, and 38% (9/24) endorsed vertigo, describing their symptoms as either "objects spinning or turning around you" or a "sensation that you are turning or spinning inside." In addition, 46% (11/24) of participants with TBI

reported imbalance, with 21% (6/24) of participants reporting a tendency to fall, 25% (5/24) reporting a history of falls, 21% (5/24) reporting difficulty navigating in well-lit spaces, and 29% (7/24) reporting difficulties navigating in dark spaces. Within the NC group, 5% (1/19) reported vertigo described as "objects spinning or turning around you," with no NC participants reporting a "sensation that you are turning or spinning inside." Similarly, only 5% (n = 1/19) of NC participants reported lightheadedness. Fisher's exact test revealed a significant association between group (TBI vs. NC) and self-reported symptoms of both vertigo and non vertigo (e.g., lightheadedness; $p = .014$; see Figure 1), with a greater percentage of the TBI group, relative to the NC group, endorsing symptoms. The TBI group was 10.8 times more likely to report vertigo compared to the NC group (OR = 10.8, 95% confidence interval [1.22, 95.22]). In addition, there was a statistically significant association between group and self-reported imbalance and/or falling ($p < 0.001$; see Figure 2.1), with a greater percentage of the TBI group, relative to the NC group, endorsing symptoms.

2.3.2. Related symptoms

Of the list of related symptoms, 63% (15/24) of participants within the TBI group most frequently endorsed headaches and were 8.8 times more likely than the NC group to report headaches ($p = 0.002$). The TBI group was also significantly more likely than the NC group to report nausea ($p < 0.01$). There were no statistically significant associations between group and symptoms of hearing loss ($p = 1.00$), emesis ($p = 0$ .086), and LOC ($p = 0.060$), suggesting that participants with TBI were no more likely than the NC group to report these symptoms (see Figure 2.1). Additionally, given the close relationship between vertigo, imbalance, and headache symptoms in common vestibular disorders (e.g., vestibular migraine), we were interested in determining whether there were any significant associations between these symptoms in participants with chronic moderate–severe TBI. For this analysis, participants who only reported headache or head pressure satisfied an overall endorsement of headache. In this sample, TBI participants with vertigo were not significantly more likely than participants with TBI who did not endorse vertigo to report symptoms of imbalance ($p = 0.155$) or headaches ($p = 0.096$).

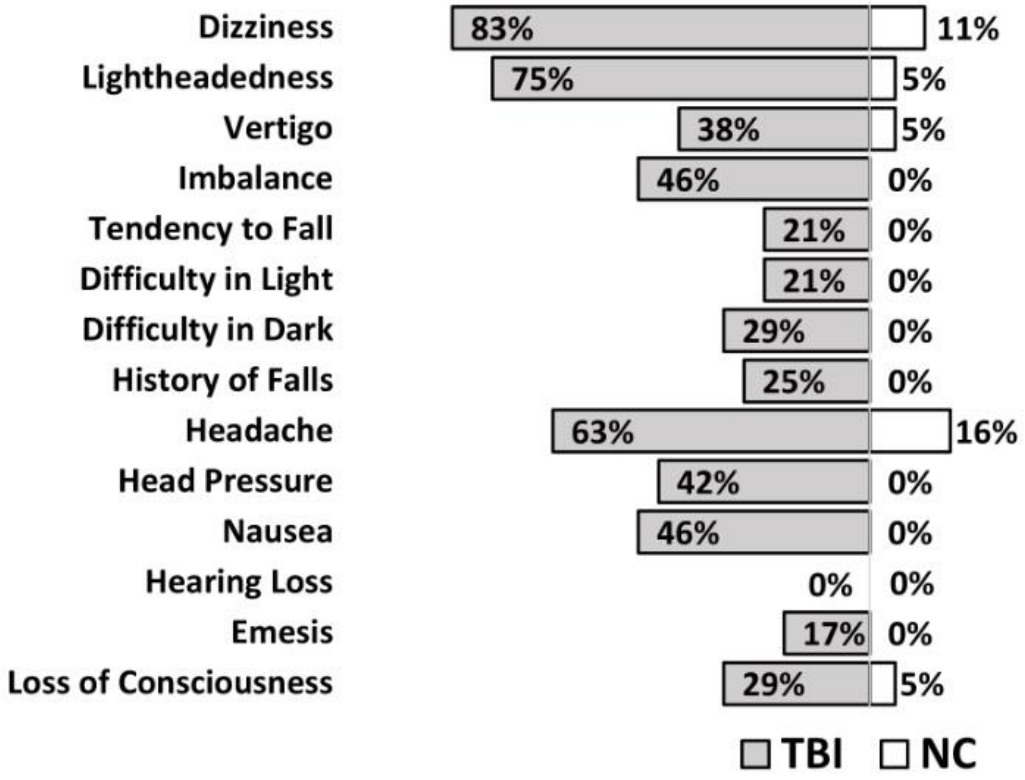

Figure 2.1. Mirror bar plot displaying the frequency of dizziness, imbalance, and related symptoms reported by the TBI (n = 24) and NC (n = 19) groups. The percentage of participants within each group who endorsed each symptom (i.e., "yes") is shown.

2.4 Discussion

The aim of this research note was to determine whether dizziness and imbalance were prevalent in a group of adults with chronic moderate–severe TBI. The case history form that was administered allowed us to (a) further describe the frequency and type of dizziness and imbalance and (b) determine if there were any significant associations between symptoms endorsed by the TBI group. The most common symptoms reported by the TBI group were lightheadedness, vertigo, and imbalance and/ or falling (see Figure 2.1). The most common related symptoms reported by the TBI group were headaches and nausea. We found that participants with TBI endorsed dizziness, imbalance, headaches, and nausea significantly more frequently than their noninjured peers. With respect to the primary scope of this research note, this

analysis serves as the first step in prospectively parsing out the frequency and type of dizziness and imbalance in adults with chronic moderate–severe TBI.

A significant percentage of participants within the TBI group reported symptoms of vertigo and/or imbalance (see Figure 2.1). While these symptoms could arise from a wide range of different conditions and locations, vertigo is a specific subtype of dizziness that is often a result of peripheral and/or central vestibular dysfunction (Baloh, 1998). Vertigo may be described as a false sense of motion with or without changes in head or body position, visually induced spinning triggered by a complex or large moving visual stimulus, and/or spinning that occurs during head movement (Lempert et al., 2022). The vestibular system is responsible for helping to maintain a clear visual image during head movement as well as contributing to the mechanisms responsible for maintaining balance (Baloh et al., 2010). The significant occurrence of vertigo and imbalance endorsed by the TBI group (38% and 46%, respectively) suggests that such symptoms are not limited to the acute phase of injury but rather persist deep into the chronic phase. Thus, chronic moderate–severe TBI may be a risk factor for an underlying, perhaps undiagnosed, vestibular impairment.

Most of our current understanding of posttraumatic vertigo and imbalance comes from retrospective studies and clinical observations in less severe cases of acute TBI (i.e., mild TBI or concussion). Nevertheless, persistent dizziness (including vertigo) and imbalance are often observed following a brain injury and traditionally thought of as a complex interaction between peripheral and central mechanisms resulting in structural and functional deficits. Peripheral causes of dizziness and imbalance in TBI may include structural damage to the inner ear labyrinth (i.e., labyrinthine concussion, perilymphatic fistulas), vestibular nerve, and otolith end organs (Akin et al., 2017; Fife&Giza,2013; Fife & Kalra, 2015; Šarkić et al., 2021). Central impairments may also co-occur (e.g., vestibular migraine) and even exacerbate symptoms when combined with psychological factors such as anxiety (i.e., persistent postural–perceptual dizziness), environmental factors, and stress-related factors (Fife & Giza, 2013; Fife & Kalra, 2015). Thus, it is difficult to parse out which mechanisms are contributing to the overwhelming endorsement of dizziness and imbalance by the participants with TBI based solely on symptoms. Given

that many of the participants with TBI reported headaches and/or head pressure, it is conceivable that vestibular migraine may be contributing, in part, to the persistent symptoms observed in the TBI group. However, objective vestibular data are needed to fully characterize peripheral vestibular function to determine its influence, if any, on participant symptoms.

Regardless of whether the origin of these symptoms is peripheral and/or central, it is relevant to clinical and research spaces. The TBI group was more than 5 years post–brain injury, on average, and while many of them did receive intervention after their injury including speech language pathology therapy, occupational therapy, and/or physical therapy for cognitive and/or physical impairments, we do not know if patients were treated for dizziness and imbalance. Determining the mechanisms underlying their persistent symptoms may help to shed light on the current identification, treatment, and rehabilitation of chronic moderate–severe TBI. The results of this research note warrant a full prospective investigation in patients with chronic moderate–severe TBI to characterize vestibular function and determine whether existing vestibular impairments can explain the persistent nature of symptoms of vertigo and imbalance in this population.

2.4.1 Study limitations, considerations, and future directions

This study consists of a small sample size and should be replicated in a larger sample of participants with chronic moderate–severe TBI given the inherent variability observed within this population. The authors acknowledge that the statistical tests performed in the study were subject to a small sample size. However, our goal with the current analysis was to help facilitate future hypothesis generation and testing in larger samples. Future prospective studies should also investigate (a) whether adults with chronic moderate–severe TBI show evidence of peripheral vestibular system impairment, (b) physiological and functional changes that occur following a chronic moderate–severe TBI, and (c) how these changes may impact quality of life, as well as determine the factors that contribute to chronic, persistent vertigo and imbalance post–brain injury.

2.4.2 Conclusions

Dizziness and imbalance are prevalent among adults with chronic moderate–severe TBI and may be indicative of an underlying, undiagnosed vestibular disorder. This study provides further justification to fully investigate the underlying cause of these symptoms in this population. Further prospective research designs are needed to adequately explore vestibular involvement once patients with TBI enter the chronic phase of injury.

CHAPTER 3

Peripheral Vestibular Function in Adults with Chronic Moderate-Severe TBI*

*This chapter is adapted from the following research article: Feller, J.J., Duff, M., Clough, S., Jacobson, G., Roberts, R. A., & Romero, D. J. (under review). Evidence of Peripheral Vestibular Impairment Among Adults with Chronic Moderate–Severe Traumatic Brain Injury. *American journal of audiology*.

3.1 Introduction

Symptoms such as dizziness and/or vertigo, which may be vestibular in origin, are among the most reported complaints among individuals with TBI (Maskell et al., 2006), as previously described. Chapter 2 described symptoms of dizziness and imbalance commonly reported in individuals with *moderate-severe* TBI in the chronic phase (>6 months post-injury), indicating this patient population may be experiencing symptoms of vestibular impairment (Romero et al., 2023). Since the vestibular system plays a crucial role in everyday life, including the coordination of gaze and postural stability, examining vestibular function in individuals experiencing dizziness and imbalance is crucial. Dizziness and imbalance can lead to an increased incidence of falls, which is a leading cause of brain injury (Friedland, Brunton, & Potts, 2014). Falls can then lead to additional brain injuries in individuals with TBI, which may lead to further vestibular, motor, and cognitive impairment, and even death (Daugherty, Waltzman, Sarmiento, & Xu, 2019).

Several areas along the vestibular pathway can be damaged concurrently with a TBI, including the semicircular canals and otolith organs of the inner ear, which can lead to dizziness and balance problems (Šarkić et al., 2021). Head trauma can cause ruptured peripheral vestibular organs (Kerr, 1975), damage to the organs' membranes, and degenerative changes in these organs (Schuknecht & Davison,

1956). Such damage could subsequently lead to functional changes in the pathways originating from the damaged organs, and evidence of peripheral vestibular impairment has been previously found in TBI populations. For example, a study of individuals with *mild* TBI in the acute phase of injury showed that 25% of the sample had evidence of otolith organ pathway impairment (Ernst et al., 2005). A second study examining individuals with *mild* TBI in the chronic phase of injury found that 25% of the sample had evidence of impairment in the pathway originating from the otolith organ, the saccule, 18% had impairment in the pathway originating from the otolith organ, the utricle, and between 5 and 8% had abnormalities in the pathway originating from the horizontal semicircular canals (Akin, Murnane, Hall, Riska, & Sears, 2022).

However, a comprehensive review of the literature revealed a substantial scarcity of prospective studies examining peripheral vestibular function following TBI and an even further paucity of experiments designed to assess vestibular function in TBI populations using standard vestibular audiology clinical methods (Maskell et al., 2006). Most studies that examine vestibular function in participants with TBI are retrospective and focus on *mild* TBI and/or TBI in the *acute* phase (<6 months post injury; for review, see (Maskell et al., 2006). Furthermore, the frequency, type, and location of vestibular impairment in individuals with *chronic moderate-severe* TBI is not well-described. There are currently no published hypothesis-driven, prospective studies investigating peripheral vestibular function in adults with chronic moderate-severe TBI. It is likely that individuals with more severe brain injuries also sustained more severe peripheral vestibular injuries compared to individuals with mild TBI. Therefore, it is important to understand the prevalence of peripheral vestibular impairment in individuals with moderate-severe TBI. Additionally, understanding the frequency, type, and location of vestibular deficits in patients with chronic moderate-severe TBI can lead to more appropriate triage, evidence-based decisions about test batteries, and comprehensive rehabilitation programs for the TBI patient population (Šarkić et al., 2021).

The aim of the study presented in Chapter 3 is to characterize the presence of peripheral vestibular impairment and its resulting symptoms in adults with chronic moderate-severe TBI, which to

date has been understudied in this population. It was hypothesized that a group of individuals with TBI would have significantly decreased peripheral vestibular function relative to a group of demographically matched non-injured individuals. Implications of this study's findings for improving assessment and rehabilitation guidelines for adults with TBI are discussed.

3.2 Methods

3.2.1 Participants

All study procedures were reviewed and approved by the Institutional Review Board (IRB, #221051) at Vanderbilt University Medical Center (VUMC). An informed consent statement was completed by all participants before testing.

A total of 30 adults (16 female; 14 male) with moderate-severe traumatic brain injury (TBI) in the chronic phase (>6 months post injury; Salmond et al., 2006) and 30 demographically matched non-injured comparison (NC) participants (16 female; 14 male) completed the study. All participants were recruited from the Vanderbilt Brain Injury Patient Registry (Duff et al., 2022) at Vanderbilt University Medical Center (VUMC). Individuals with and without a history of TBI were invited to participate in the Registry using a variety of methods (institutional mass e-mail, social media, flyers, word of mouth, mailers). For more detailed information about the registry, see Duff et al. (2022). All Registry members with TBI who met the inclusion criteria were invited to participate in the study. NC Registry members who were demographically matched to at least one of the participants with TBI were invited to participate. All participants were between the ages of 18 and 55 years at the time of testing to limit possible confounding effects of expected age-related vestibular and cognitive decline (Iwasaki & Yamasoba, 2015; Salthouse, 2009).. Participants with TBI were at least 18 years of age at the onset of their injury to limit potentially confounding effects of developmental changes.

Participants with TBI each sustained a single brain injury to limit possible confounding effects of multiple injuries. Each TBI was classified as moderate-severe using the Mayo Classification System

(Malec et al., 2007). Each participant with TBI met at least the following criteria: (1) Glasgow Coma Scale (GCS) <13 within the first 24 hours (acute phase), (2) loss of consciousness (LOC) >30 minutes, (3) post-traumatic amnesia (PTA) >24 hours, and/or (4) positive CT findings in the acute phase and/or visible lesions on MRI during the chronic phase. Medical records were used to determine TBI information. A semi-structured participant interview was completed to confirm injury information. Participants with TBI had no history of hearing, neurological, or cognitive disorders. Participants with TBI were matched pairwise to NC participants on sex, age (+/- 5 years), and years of completed education (+/- 2 years) to reduce the variability between the NC and TBI groups. Comparison participants reported no history of hearing, vestibular, neurological, or cognitive impairments. Participants who reported current use of medications that are known to affect vestibular function (e.g., meclizine) were excluded from the study.

NC participants ranged in age from 20 to 53 years (mean = 36.7, SD = 9.62), and participants with TBI ranged in age from 24 to 55 years (mean = 36.8, SD = 9.97). Years of completed education for participants in the NC and TBI groups ranged from 12 to 20 (NC: mean = 14.53, SD = 2.46; TBI: mean = 14.67, SD = 2.43). There were no statistically significant differences between the NC and TBI groups for age ($z = 0.044$, $p = 0.965$) or years of education ($z = -2.08$, $p = 0.835$). Demographic and injury information for the NC and TBI groups is shown in Table 3.1. For the TBI group, time post-injury ranged from 8 to 276 months (mean = 71.53, SD = 70.49), and Glasgow Coma Scale (GCS) values ranged from 3 to 15 (mean = 9.35, SD = 4.85). Demographic and injury information for each participant with TBI is shown in Table 3.2.

TABLE 3.1. Demographic and injury information for NC and TBI groups.

	NC Group (N = 30)				TBI Group (N = 30)			
	n (%)	**Mean**	**SD**	**Range**	**n (%)**	**Mean**	**SD**	**Range**
Age (years)		36.7	9.62	20 - 53		36.8	9.97	24 - 55
EDU (years)		14.53	2.46	12 - 20		14.67	2.43	12 - 20
Sex (female)	16 (53)				16 (53)			
TSO (months)		n/a				71.53	70.49	8 - 276
GCS		n/a				9.35	4.85	3 - 15

Note: EDU, Completed education; GCS, Glasgow Coma Scale score; TSO, time since onset of TBI

TABLE 3.2. Demographic and injury information for each participant with TBI.

Participant	Sex	Age (years)	EDU	TSO	GCS	Etiology	LOC	PTA	Neuroimaging
1	F	21-25	12	13	14	MVA	N/A	> 24 hrs	SAH
2	F	36-40	16	77	3	MVA	> 30 min	> 24 hrs	SAH
3	F	21-25	12	61	13	MVA	> 30 min	> 24 hrs	SAH
4	F	51-55	12	29	15	Ground-level fall	No LOC	No PTA	SAH, SDH
5	M	31-35	18	57	15	Ground-level fall	> 30 min	< 24 hrs	SAH, IPH
6	F	31-35	16	18	15	MVA	< 30 min	N/A	SAH
7	M	31-35	12	14	7	MVA	> 30 min	> 24 hrs	SAH
8	M	41-45	12	69	3	Other	> 30 min	> 24 hrs	ICH, PCH, SAH, SDH
9	F	41-45	18	74	3	MVA	> 30 min	> 24 hrs	EDH, SAH
10	M	26-30	16	24	3	Ped vs. auto	> 30 min	> 24 hrs	EDH, SAH, SDH
11	F	31-35	16	98	10	MVA	No LOC	> 24 hrs	No acute intracranial findings
12	M	26-30	12	8	7	MCC	> 30 min	> 24 hrs	Shear/DAI
13	F	46-50	16	75	6	Ped vs. auto	N/A	> 24 hrs	SAH, SDH
14	M	26-30	12	13	15	Ped vs. auto	No LOC	< 24 hrs	IPH, SAH, SDH, hemorrhagic contusions
15	F	41-45	12	117	3	MVA	> 30 min	> 24 hrs	SAH, SDH, uncal herniation
16	M	36-40	20	49	15	Struck by object	< 30 min	< 24 hrs	SDH, scattered SAH, right temporal hemorrhage
17	F	31-35	14	50	9	MVA	< 30 min	> 24 hrs	SAH, SDH
18	M	51-55	12	276	N/A	MVA	> 30 min	> 24 hrs	Hemorrhage
19	F	51-55	16	50	14	MVA	< 30 min	< 24 hrs	SAH, SDH
20	F	36-40	16	250	N/A	MVA	> 30 min	> 24 hrs	SAH, possible right frontal contusion
21	M	51-55	16	237	N/A	MVA	> 30 min	> 24 hrs	N/A
22	F	46-50	16	72	9	MVA	< 30 min	> 24 hrs	SDH, PCH, arachnoid hemorrhage
23	M	46-50	16	25	3	Fall from height	> 30 min	> 24 hrs	SAH
24	M	21-25	12	10	3	MVA	> 30 min	> 24 hrs	ICH, IVH, PCH, SAH, SDH, DAI
25	F	26-30	18	72	10	MVA	> 30 min	> 24 hrs	SDH
26	M	36-40	16	130	15	Ped vs. auto	> 30 min	< 24 hrs	SAH
27	M	31-35	16	22	15	Ground-level fall	N/A	> 24 hrs	SAH, SDH, Bifrontal contusions
28	M	26-30	12	25	10	MVA	> 30 min	> 24 hrs	SDH, PCH, DAI
29	F	26-30	16	106	N/A	MVA	< 30 min	> 24 hrs	Shear injury, DAI
30	F	21-25	12	25	8	Other	> 30 min	> 24 hrs	SAH, SDH

Note: Education (EDU) reflects years of highest degree obtained; MCC includes both motorcycle and snowmobile accidents; Time since injury onset (TSO) is presented in months; Loss of consciousness (LOC) is presented in minutes; Glasgow Coma Scale (GCS) is total score at the time of first postinjury measurement; PTA = post-traumatic amnesia; MVA = motor vehicle accident; N/A = information was not available; SAH = subarachnoid hemorrhage; Ped vs. auto = participant was hit by a car while walking or running; SDH = subdural hematoma; EDH = epidural hematoma; PCH = parenchymal hemorrhage; IPH = intraparenchymal hemorrhage; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; DAI = diffuse axonal injury.

3.2.2 Self-report questionnaires

All participants first completed a case history form using a paper and pencil method to assess whether they experienced vestibular symptoms. The case history form administered was a modified version of a standard case history form (Furman, Cass, & Whitney, 2010). This 24-item form allowed the participant to report the presence, type, and description of any concerning symptoms that may be vestibular in origin (e.g., dizziness, imbalance). Each participant was asked to endorse (by checking "yes") any active symptoms and to deny (by checking "no") any symptoms not currently experienced.

Two self-report questionnaires were administered to all participants with TBI to get a better understanding of their dizziness and balance-related quality of life. Participants completed the Dizziness Handicap Inventory (DHI) using a paper and pencil method of administration (Jacobson & Newman, 1990). The DHI is a 25-item standardized reliable and valid questionnaire of self-perceived handicap associated with dizziness (Jacobson & Newman, 1990) and has minimal floor and ceiling effects (Enloe & Shields, 1997). Each item on the DHI was scored according to the following point system: "no" (scored as 0 points), "sometimes" (scored as 2 points), and "yes" (scored as 4 points) (Jacobson & Newman, 1990). Item scores were added to calculate a total dizziness handicap score, with a maximum total score of 100 points. A total score of 14 or less was considered no handicap, a score between 16 and 26 was considered a mild handicap, a score between 28 and 44 was considered a moderate handicap, and a score of 46 or greater was considered a severe handicap (Jacobson & Newman, 1990).

A total of 27 participants with TBI completed the Activities-specific Balance Confidence (ABC) scale using the pencil and paper method (Powell & Myers, 1995). The ABC is a 16-item structured self-report questionnaire of confidence in maintaining balance during performance of various common ambulatory activities (Powell & Myers, 1995). The ABC correlates with the Community Balance and Mobility (CB&M) Scale, a clinical measure of balance that has been validated in patients with TBI (Hays et al., 2019; Inness et al., 2011). Each item on the ABC was scored according to the following point system: 0% (no confidence) to 100% (complete confidence) in 10% increments (Powell & Myers, 1995). Unlike the previous questionnaires, smaller scores on the ABC scale represented greater impairment, as

smaller percentages represented less confidence maintaining balance during specific activities. A score lower than 50% was considered low-level functioning, a score of 50-80% was considered moderate-level functioning, and a score above 80% was considered high-level functioning (Myers, Fletcher, Myers, & Sherk, 1998).

3.2.3 Vestibular tests

All participants underwent vestibular function testing. Prior to testing, otoscopy was completed for each participant to ensure clear ear canals and visibility of the tympanic membranes of both ears. Participants then completed cervical and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs), video head impulse test (vHIT), and ocular motor testing using videonystagmography (VNG). Each participant completed all vestibular tests on the same day within an approximate 1-hour period. The order of the four tests, as well as the order of ear stimulation during VEMPs, was randomized to reduce the possibility of an order effect. An ocular motor assessment was used to rule out possible impairments that may not be peripheral vestibular in origin. Gaze, saccade, optokinetic, smooth pursuit, and spontaneous nystagmus ocular motor tests were completed. Only participants who showed normal ocular motor results were included in this study. One recruited participant with TBI showed evidence of nystagmus during ocular motor testing, was excluded from the study, and was not included in the final sample. All NC participants tested showed normal ocular motor results.

3.2.3.1 Vestibular evoked myogenic potentials (VEMPs)

All participants completed cVEMPs and oVEMPs, which were used to measure activity originating from the saccule and utricle of each ear, respectively (for review, see Rosengren et al., 2019). VEMPs were recorded using disposable multipurpose Ag/AgCl snap electrodes. All data were collected using Neuroscan SCAN software (Version 4.5). The stimulus used for all VEMPs was an air-conducted (AC) 500 Hz Blackman tone burst with a rise fall time of 2 ms and a plateau duration of 0 ms. All tone bursts were presented at 125 dB peak SPL at a rate of 5.4 per second. Right and left ears were tested

separately in a closed-field procedure using ER3A insert earphones. For each ear, two recordings of 130 presentations were collected and averaged together. VEMPs were recorded with a response window of -20 to 80 ms and a sampling rate of 20 kHz. Recorded VEMP signals were digitally filtered from 5 to 1500 Hz.

For cVEMPs, the active electrode was placed on the belly of the sternocleidomastoid muscle (SCM) ipsilateral to the ear being tested, the reference electrode was placed at the sternoclavicular notch, and the ground electrode was placed on the forehead. Participants laid in a supine position throughout cVEMP testing. During data collection, participants were instructed to keep their head raised from the table and turned away from the ear being stimulated. Electrodes were routed to a commercially available multichannel evoked potential system (Intelligent Hearing System Smart EP; Version 5.20). A second video monitor enabled participants to adjust their muscle tone to meet fixed EMG targets during recording. The EMG was amplified (x 2000) and filtered (5-1500 Hz). The recording system displayed a bar graph representing the magnitude of the tonic mean rectified EMG over time. The objective was for the participants to maintain the EMG at 50 μV (+/- 10), which was clearly marked on the bar graph.

The electrode montage for oVEMPs consisted of one multipurpose snap electrode placed near each of the inferior oblique muscles, one ground electrode on the forehead, and one reference electrode on each inner canthus of the eye (Sandhu, George, & Rea, 2013). Recordings were made from the side contralateral to the ear being stimulated. Participants were seated upright in a chair and instructed to maintain their gaze (without moving their head) on a visual target set at a 30˚ gaze angle elevated in front of them. Tympanometry was completed on ears with absent VEMP responses to reduce the likelihood of VEMP wave absence due to impaired middle ear status. All tympanometry results were within the normal range.

VEMP responses were visually inspected and analyzed offline using a custom MATLAB program (JF/DR). A post-hoc bandpass filter from 10-300 Hz was applied to each recording to reduce noise artifacts offline. cVEMPs were defined as “present” if there was a positive deflection near 13 ms (p1), a negative deflection near 23 ms (n1), and a repeatable response above the noise floor (Rosengren,

Colebatch, Young, Govender, & Welgampola, 2019). The noise floor was defined as the average amplitude of the recording prior to stimulus onset (-20 to 0 ms). After p1 and n1 were visually detected and labeled, response rate, p1 and n1 latencies, p1n1 amplitudes, raw EMG amplitude, and corrected amplitude were tabulated. Mean rectified EMG amplitudes were measured offline by taking the average EMG amplitude across each sweep. Corrected amplitude was calculated by dividing the peak-to-peak amplitude by the mean rectified EMG amplitude. oVEMPs were considered present if there was a negative deflection between 10 and 12 ms (n1), a positive deflection between 15 and 17 ms (p1), and a repeatable response above the noise floor (Rosengren et al., 2019). After n1 and p1 were visually detected and labeled, response rate, n1 and p1 latencies, and n1p1 amplitudes were calculated. VEMP responses were considered absent if no reproducible wave was present. Asymmetry ratios for oVEMP amplitude and cVEMP corrected amplitude were calculated according to the following formula:

$$AR = \frac{|\,(left\ p1 - n1\ amplitude) - (right\ p1 - n1\ amplitude)|}{|\,(left\ p1 - n1\ amplitude) + (right\ p1 - n1\ amplitude)|}\ x100$$

Participants with unilaterally absent VEMP responses were considered to have 100% amplitude asymmetry (Akin et al., 2022).

3.2.3.2 Video head impulse test (vHIT)

A total of 29 TBI and 29 NC participants completed video head impulse test (vHIT), which was used to measure vestibulo-ocular reflex (VOR) activity originating from the horizontal semicircular canal of each ear (for review, see Alhabib & Saliba, 2017). One TBI and one NC participant from the cohorts who completed VEMPs were unable to complete vHIT due to video interference resulting in difficulty with eye tracking. All participants who completed vHIT also completed oVEMPs and cVEMPs. For each participant, vHIT was completed using the Otometrics ICS Impulse® vHIT program. For this test, each participant was instructed to fixate on a one-inch target approximately 1 m in front of their eyes while an experimenter moved the participant's head in short (~15˚), fast (>150 degrees per second), unpredictable motions in the plane of the horizontal semicircular canals (Halmagyi et al., 2017). Video goggles worn by

the participant recorded the instantaneous compensatory eye movements as a response to each head impulse.

All vHIT traces were visually inspected and analyzed offline using the Otometrics ICS Impulse® program. For each head impulse, the Otometrics ICS Impulse® program provided figures showing head velocity and eye velocity as a function of time, resulting in one curve for head velocity and a second curve for eye velocity. VOR gain, or the ratio between compensatory eye movement velocity (area under the eye velocity curve) and head impulse velocity (area under the head velocity curve). This ratio was calculated for each of the horizontal semicircular canals (left and right ear) by the Otometrics ICS Impulse® program. Traces were visually inspected for corrective saccades, defined as saccades occurring during or after the head impulse, indicating impaired VOR function (MacDougall, Weber, McGarvie, Halmagyi, & Curthoys, 2009).

3.2.4 Statistical Analysis

MATLAB version R2023a was used for all statistical analyses. Descriptive statistics were used to determine the mean and standard deviation for the NC and TBI groups for age, years of education, and the following variables when responses were present: oVEMP and cVEMP peak-to-peak amplitude, oVEMP and cVEMP p1 and n1 latency, cVEMP corrected amplitude, oVEMP amplitude asymmetry, cVEMP corrected amplitude asymmetry, and VOR gain. For all of these variables, normality was violated according to the Kolmogorov-Smirnov test (*kstest* function in MATLAB; for overview, see Berger & Zhou, 2014), thus only nonparametric tests were used and reported. Wilcoxon rank-sum tests (*ranksum* function in MATLAB; Wilcoxon, Katti, & Wilcox, 1970) were used to determine group differences for each variable for the participants with TBI with present responses and their NC matches. An alpha level of 0.05 was used to determine significance for all statistical tests, except the cVEMP and oVEMP variables. For cVEMP variables, a Bonferroni correction (Armstrong, 2014) was used to adjust the alpha level to 0.01 to account for the five hypotheses tested from the same cVEMP assessment. Likewise, for the oVEMP variables, a Bonferroni correction was used to adjust the alpha level to 0.0125 to account for

the four hypotheses tested from the same oVEMP assessment.

Since VEMP amplitude asymmetry ratios, VEMP absence, and vHIT VOR gain are used to clinically determine VEMP and vHIT abnormality, these variables were further examined. First, normative cutoff values for vHIT VOR gain and oVEMP and cVEMP amplitude asymmetry were calculated from this study's group of NC participants. Although clinical cutoff values for VEMP amplitude asymmetry have been previously established, asymmetry ratios can vary greatly across clinical centers (Strupp et al., 2020). Similarly, although clinical cutoff values for VOR gain have been previously established, these values are based on participant samples with age ranges beyond that of our study, and are therefore not directly comparable to our participant sample (Blödow, Pannasch, & Walther, 2013; MacDougall et al., 2009). Consistent with clinical standards, 95% confidence intervals (CI) of normative data were used to calculate cutoff values (Blakley & Wong, 2015) to determine whether amplitude asymmetry and VOR gain for each participant was considered normal or abnormal. For oVEMP amplitude asymmetry and cVEMP corrected amplitude asymmetry, the cutoff for a normal response was defined as the value two standard deviations above the mean (95% CI) of the NC data. Any asymmetry value above the cutoff was considered an abnormal amplitude asymmetry. Abnormal VEMP response was defined as any response that was absent or had abnormal amplitude asymmetry. For vHIT VOR gain, the cutoff for a normal response was defined as the value two standard deviations below the mean (95% CI) of the NC data. Abnormal vHIT response was defined as any response with a VOR gain below the cutoff with the presence of corrective saccades (Blödow et al., 2013; MacDougall et al., 2009).

3.3 Results

3.3.1 Self-report questionnaires

From the case history form, the percentage of participants in the TBI group who endorsed symptoms that could be associated with vestibular impairment were as follows: 80% (24/30) dizziness, 63% (19/30) headaches, 47% (14/30) nausea, 43% (13/30) imbalance, 37% (11/30) head pressure, 20%

(6/30) falls, and 17% (5/30) emesis. Participants who reported dizziness were asked to report whether they experienced lightheadedness and/or vertigo; 73% (22/30) reported lightheadedness, and 47% (14/30) reported vertigo. The mean DHI score for the TBI group was 17.7 (*SD* = 18.7). DHI scores indicated that 13% (4/30) of participants with TBI had self-reported severe dizziness handicap (score ≥46), 13% (4/30) had moderate handicap (scores 28-44), and 10% (3/30) had mild handicap (scores 16-26). The mean ABC score for the TBI group was 79.8 (*SD* = 25.1). ABC scores, self-reports of balance confidence, revealed that 15% (4/27) of participants with TBI self-reported low-level balance functioning (scores below 50%) and 15% (4/27) had moderate-level functioning (scores 50-80%). Overall, these results indicate that a significant proportion of participants with chronic moderate-severe TBI self-report symptoms of dizziness and imbalance, as well as decreased quality of life related to these symptoms.

3.3.2 Vestibular tests

3.3.2.1 Cervical vestibular evoked myogenic potentials (cVEMPs)

The effect of moderate-severe TBI on the vestibular pathway originating from the saccule was assessed using cVEMPs, which were completed on all participants. Figures 3.1a and 3.1b show the grand average waveforms for the NC and TBI groups, respectively. Bilaterally present cVEMP responses were found for 97% (29/30) of NC participants and 87% (26/30) of the participants with TBI. All 5 cVEMP absences across both groups were unilateral.

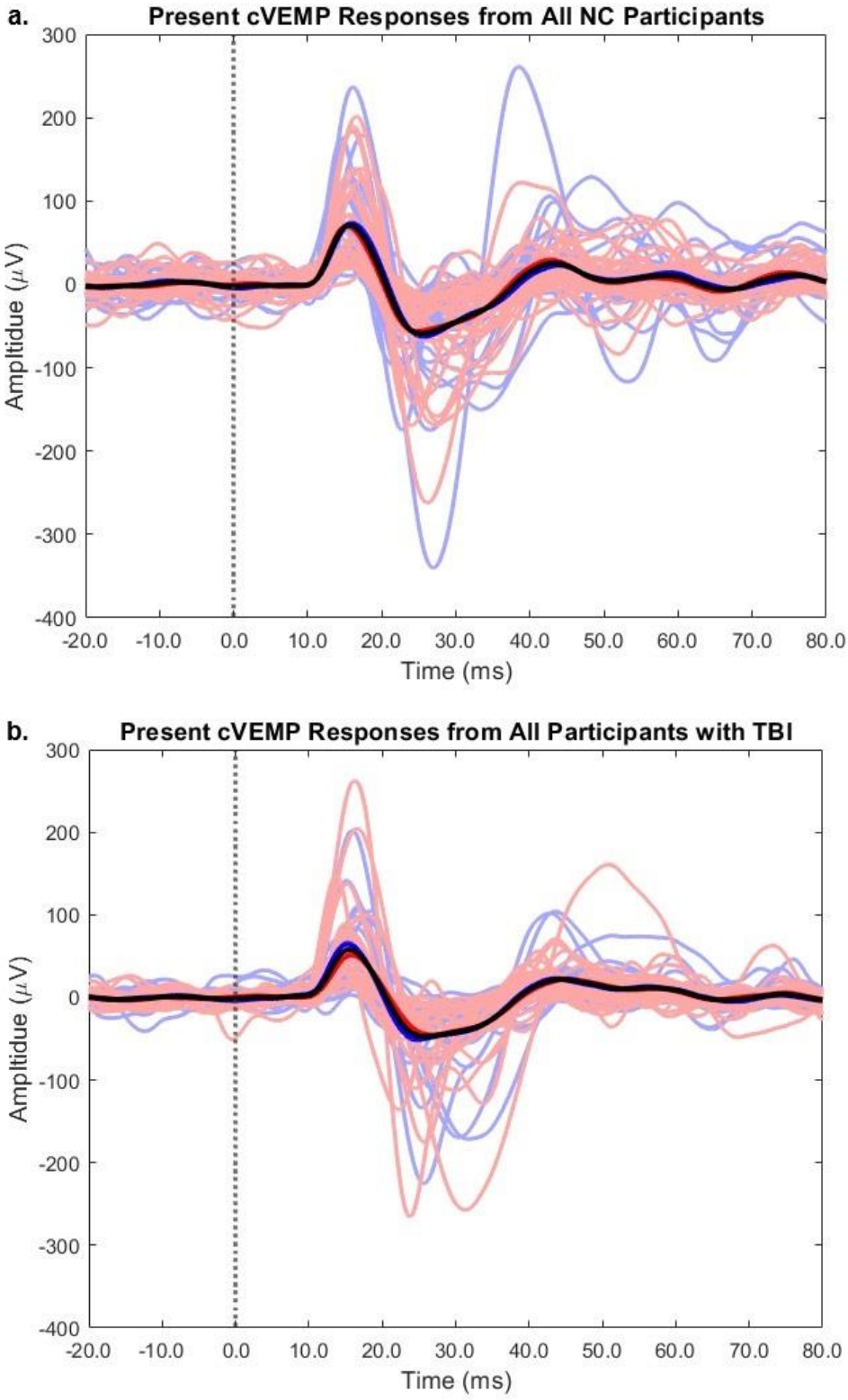

Figure 3.1. Present cVEMP response waveforms for all (a) NC participants and (b) participants with TBI. Individual response waveforms are shown in light blue (left ear) and light red (right ear). Group average responses are shown in dark blue (left ear) and red (right ear). Grand average waveforms across both ears are shown in black.

Table 3.3 shows the mean and standard deviation for the NC and TBI groups, as well as results of the Wilcoxon rank-sum tests to determine group differences for the following cVEMP variables: peak-to-peak amplitude, p1 and n1 latencies, corrected amplitude, and corrected amplitude asymmetry. Using an adjusted alpha level of 0.01, statistically significant differences between the NC and TBI groups were found only for cVEMP corrected amplitude asymmetry ($z = -3.581$, $p < 0.001$), while no statistically significant group differences were observed for cVEMP peak-to-peak amplitude, p1 or n1 latencies, or corrected amplitude.

TABLE 3.3 Descriptive statistics and Wilcoxon rank-sum differences between the NC and TBI groups.

Measure	NC Group		TBI Group		*Z*	ranksum	*p*
	Mean	SD	Mean	SD			
cVEMP							
p1-n1 Amplitude (μV)	152.73	111.76	127.91	109.02	1.393	3286	0.164
Corrected Amplitude (μV)	2.07	1.26	2.10	1.87	0.365	3114	0.715
n1 Latency (ms)	25.31	2.33	25.56	3.04	-0.200	3019	0.841
p1 Latency (ms)	15.85	1.34	15.77	1.63	0.694	3169	0.488
Corrected Amplitude Asymmetry (%)	12.81	9.48	27.91	17.93	-3.581	673	< 0.001*
oVEMP							
n1-p1 Amplitude (μV)	7.40	5.52	9.44	8.82	-0.988	2012	0.323
n1 Latency (ms)	11.15	0.84	11.35	0.94	-0.793	2037	0.428
p1 Latency (ms)	16.08	1.36	16.16	1.48	-0.340	2095	0.734
Amplitude Asymmetry (%)	19.02	13.43	27.90	17.97	-3.276	553	0.001*
vHIT							
VOR Gain	1.01	0.07	1.02	0.12	-1.108	3192	0.268

Note: cVEMP = cervical vestibular evoked myogenic potentials; oVEMP = ocular vestibular evoked myogenic potentials; vHIT = video head impulse test; SD = standard deviation; asterisk (*) denotes statistical significance

Figure 3.2 shows cVEMP corrected amplitude asymmetry for the 30 NC participants and 30 participants with TBI with present or unilaterally absent cVEMP responses. For the NC group, corrected amplitude asymmetry for present responses ranged from 0.13% to 27.89% ($M = 12.81\%$, $SD = 9.48\%$). One NC participant had a unilaterally absent response, and therefore, 100% corrected amplitude

asymmetry. For the TBI group, corrected amplitude asymmetry for present responses ranged from 2.58% to 62.27% (*M* = 27.91%, *SD* = 17.93%). Four participants with TBI had unilaterally absent responses, and therefore, 100% corrected amplitude asymmetry.

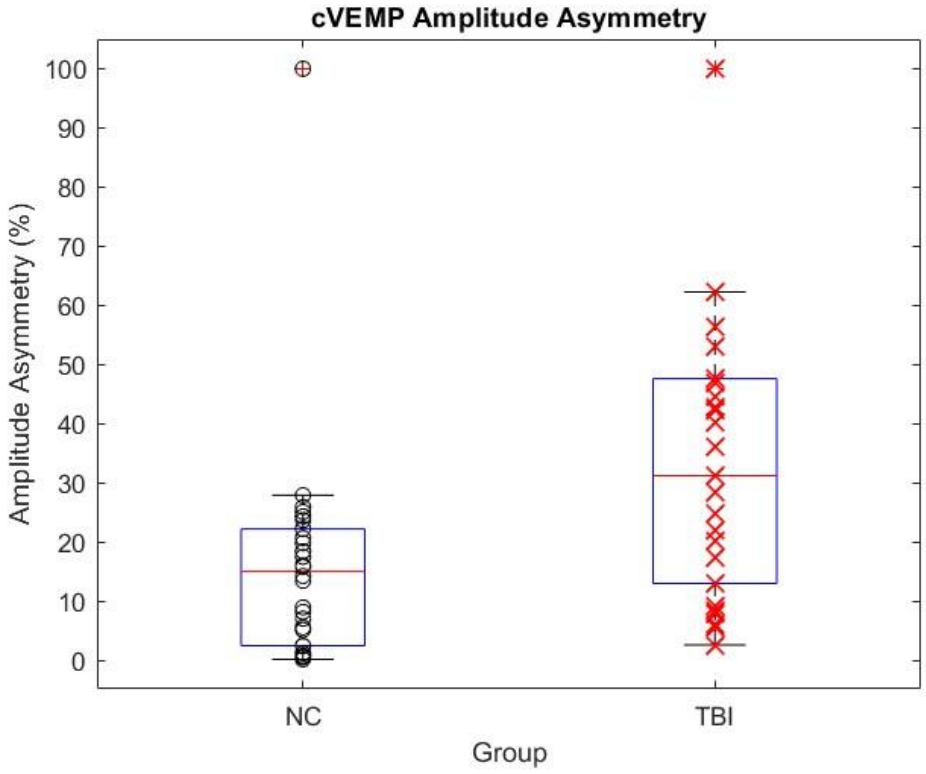

Figure 3.2. cVEMP corrected amplitude asymmetry as a function of group. Asymmetry for each NC participant is denoted by a gray "o", and asymmetry for each participant with TBI is denoted by a red "x." Boxplots show the median and second and third quartiles.

Finally, the proportion of normal and abnormal cVEMP responses per group was determined (Figure 3.3) for present responses. Cutoff values for abnormal corrected amplitude asymmetry were defined as values above the 95% CI of the NC data. The 95% CI cutoff for normative cVEMP corrected amplitude asymmetry was found to be 31.76%. Results indicated that none (0/30) of the NC participants and 33% (10/30) of participants with TBI had present responses with cVEMP corrected amplitude asymmetries above the normative cutoff. Abnormal cVEMP responses (including abnormal amplitude

asymmetry and absent responses) accounted for 3% (1/30) of the NC group and 47% (14/30) of the TBI group.

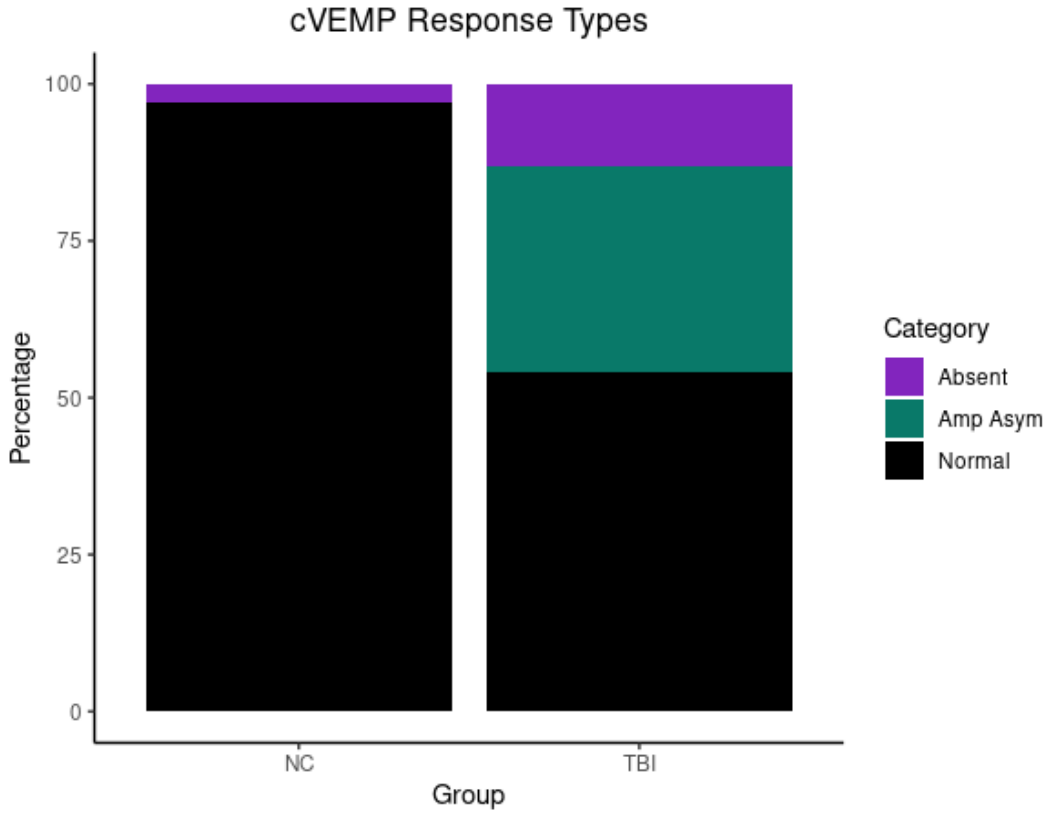

Figure 3.3. cVEMP response types as a function of group. The percentage of participants with each response type are denoted by the following colors: absent = purple, amplitude asymmetry = green, normal responses = black.

3.3.2.2 Ocular vestibular evoked myogenic potentials (oVEMPs)

The effect of moderate-severe TBI on the vestibular pathway originating from the utricle was assessed using oVEMPs, which were completed with all participants. Figures 3.4a and 3.4b show the grand average waveforms for the NC and TBI groups, respectively. Bilaterally present oVEMP responses were found for 100% (30/30) of NC participants but only 63% (19/30) of participants with TBI. 27% (8/30) of participants with TBI had unilaterally absent oVEMPs, and 10% (3/30) of participants with TBI had bilaterally absent oVEMPs.

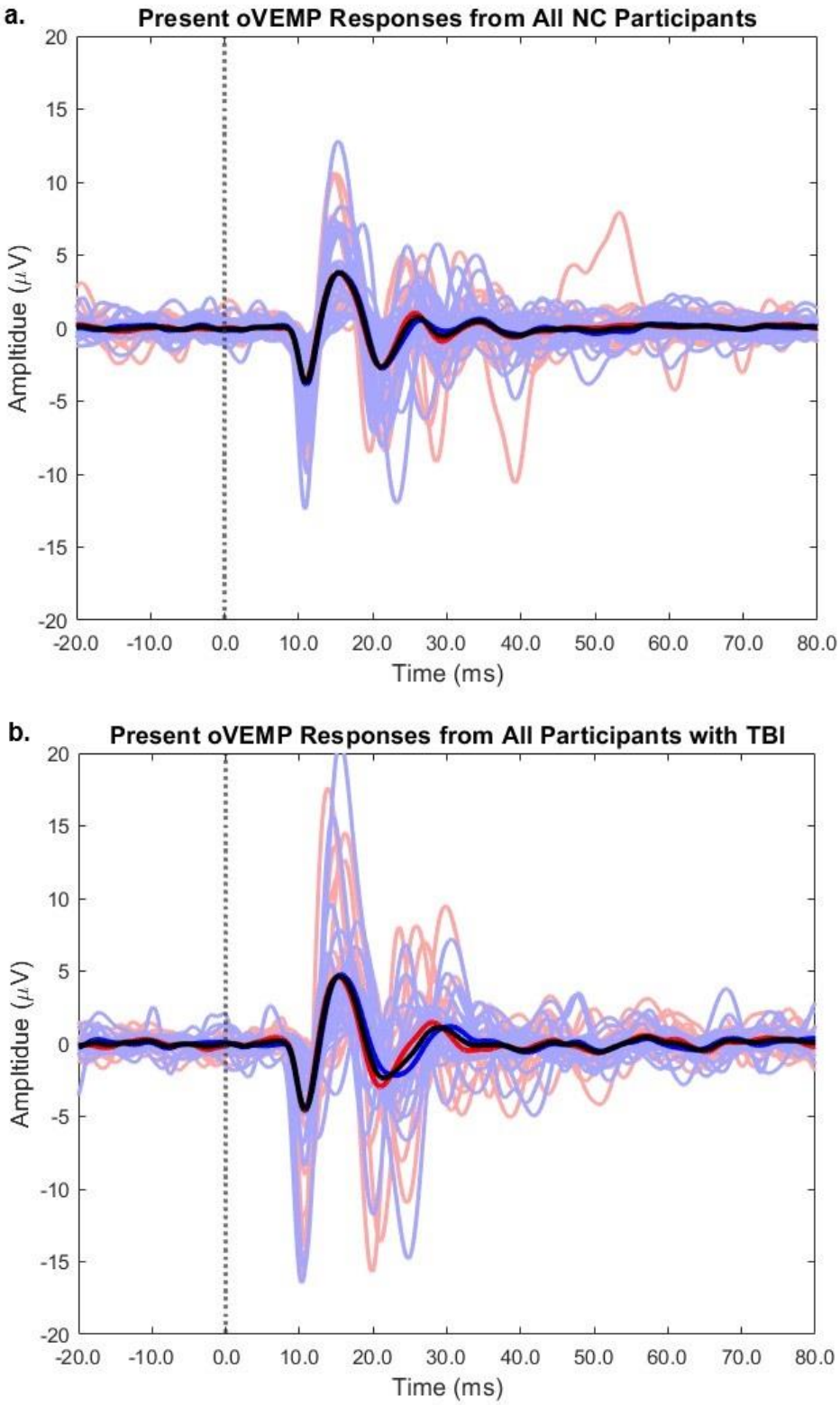

Figure 3.4. Present oVEMP response waveforms for all (a) NC participants and (b) participants with TBI. Individual response waveforms are shown in light blue (left ear) and light red (right ear). Group average responses are shown in dark blue (left ear) and red (right ear). Grand average waveforms across both ears are shown in black.

Table 3.3 shows the mean and standard deviation for the NC and TBI groups, as well as results of the Wilcoxon rank-sum tests to determine group differences for the following oVEMP variables: peak-to-peak amplitude, p1 and n1 latencies, and amplitude asymmetry. Using an adjusted alpha level of 0.0125, statistically significant differences between the NC and TBI groups were found only for oVEMP amplitude asymmetry ($z = -3.276$, $p = 0.001$), while no statistically significant group differences were observed for oVEMP peak-to-peak amplitude or p1 or n1 latencies.

Figure 3.5 shows oVEMP amplitude asymmetry for the 30 NC and 27 TBI participants with present or unilaterally absent oVEMP responses. For the NC group, amplitude asymmetry of present responses ranged from 1.06% to 63.11% (M = 19.02%, SD = 13.43%). However, the single NC participant with 63.11% oVEMP amplitude asymmetry was found to be an outlier (*isoutlier* function in MATLAB). Eliminating this data point resulted in an amplitude asymmetry range of 1.06% to 38.72% (mean = 17.50%, SD = 10.72%) for the NC group. For the TBI group, amplitude asymmetry for present responses ranged from 2.29% to 63.06% (M = 27.90%, SD = 17.97%). No statistical outliers were found for the present responses of the TBI group. Eight participants with TBI had unilaterally absent responses, and therefore, 100% amplitude asymmetry.

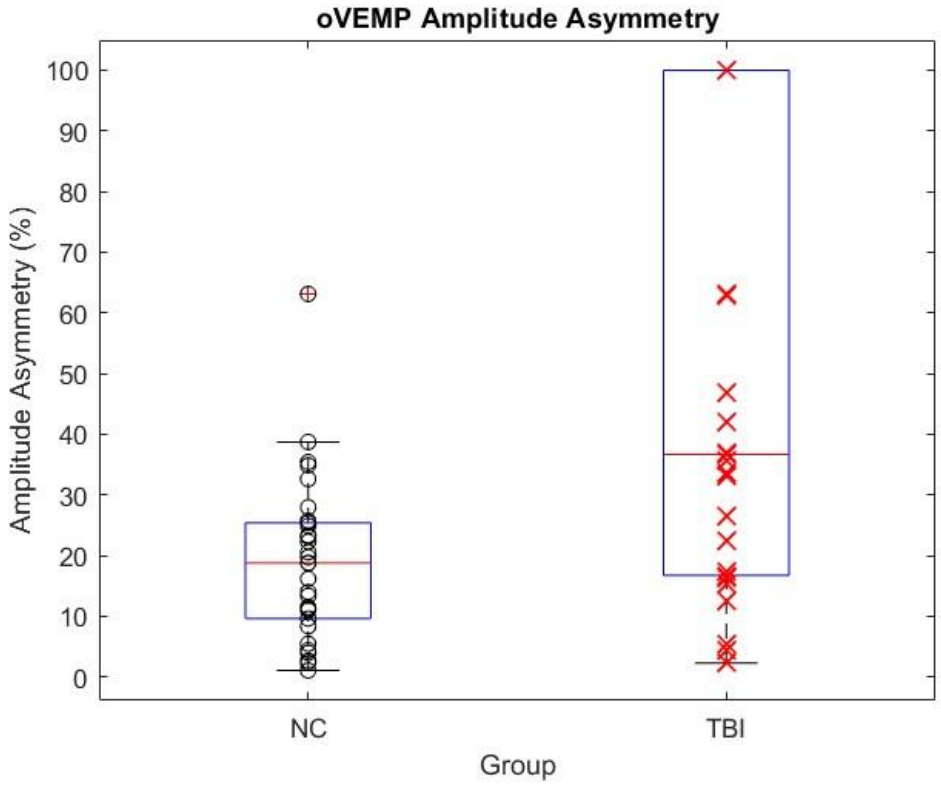

Figure 3.5. oVEMP amplitude asymmetry a function of group. Asymmetry for each NC participant is denoted by a gray "o", and asymmetry for each participant with TBI is denoted by a red "x." Boxplots show the median and second and third quartiles.

Finally, the proportion of normal and abnormal oVEMP responses per group was determined (Figure 3.6) for present responses. Cutoff values for abnormal amplitude asymmetry were defined as values above the 95% CI of the NC data. The 95% CI cutoff for normative oVEMP amplitude asymmetry was found to be 38.72%. Results indicated that 3% (1/30) of NC participants and 13% (4/30) of TBI participants had present responses with oVEMP amplitude asymmetries above the normative cutoff. Abnormal oVEMP responses (including abnormal amplitude asymmetry and absent responses) accounted for 3% (1/30) of the NC group and 50% (15/30) of the TBI group.

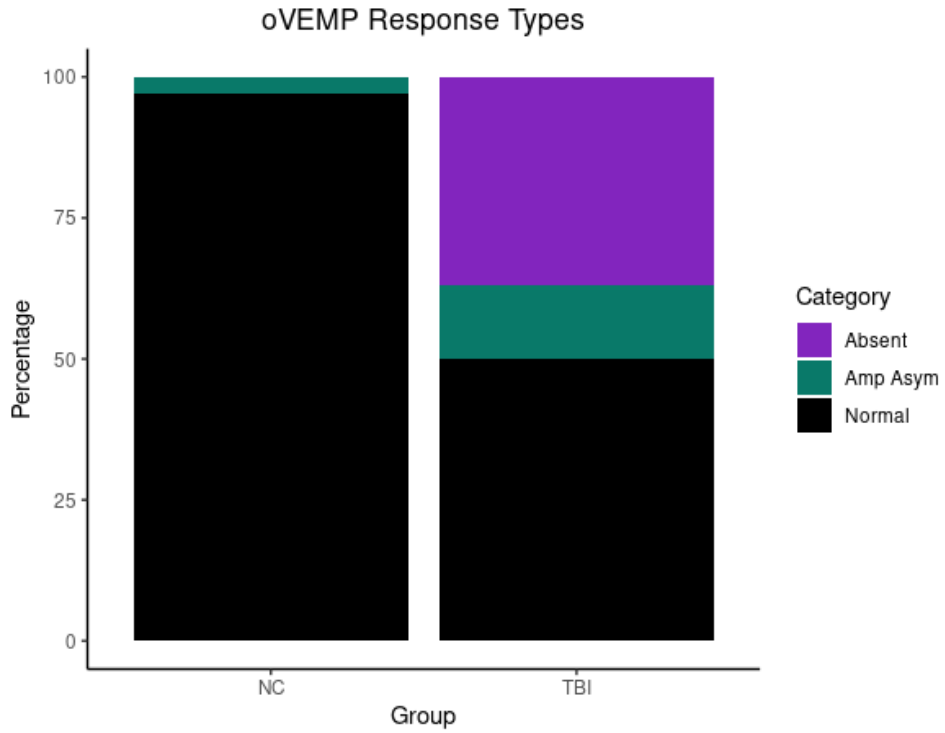

Figure 3.6. oVEMP response types as a function of group. The percentage of participants with each response type are denoted by the following colors: absent = purple, amplitude asymmetry = green, normal responses = black.

3.3.2.3 Video head impulse test (vHIT)

The effect of moderate-severe TBI on the vestibular pathway originating from the horizontal semicircular canal was assessed using video head impulse test (vHIT). Vestibular-ocular reflex (VOR) gain was calculated from vHIT for 29 NC and 29 TBI participants. Figure 3.7 shows VOR gain for all 29 NC and 29 TBI participants. For the NC group, VOR gain ranged from 0.87 to 1.19 (M = 1.01, SD = 0.07). For the TBI group, VOR gain ranged from 0.75 to 1.37 (M = 1.02, SD = 0.12). Cutoff values for VOR gain were defined as values below the 95% CI of the NC data. The 95% CI cutoff for normative VOR gain was found to be 0.87. None (0/29) of the NC participants and only 10% (3/29) of the participants with TBI had VOR gains less than 0.87 with the presence of corrective saccades. Table 2 shows the results of Wilcoxon rank-sum test, which revealed no statistically significant group differences in VOR gain (z= -1.108, p = 0.268).

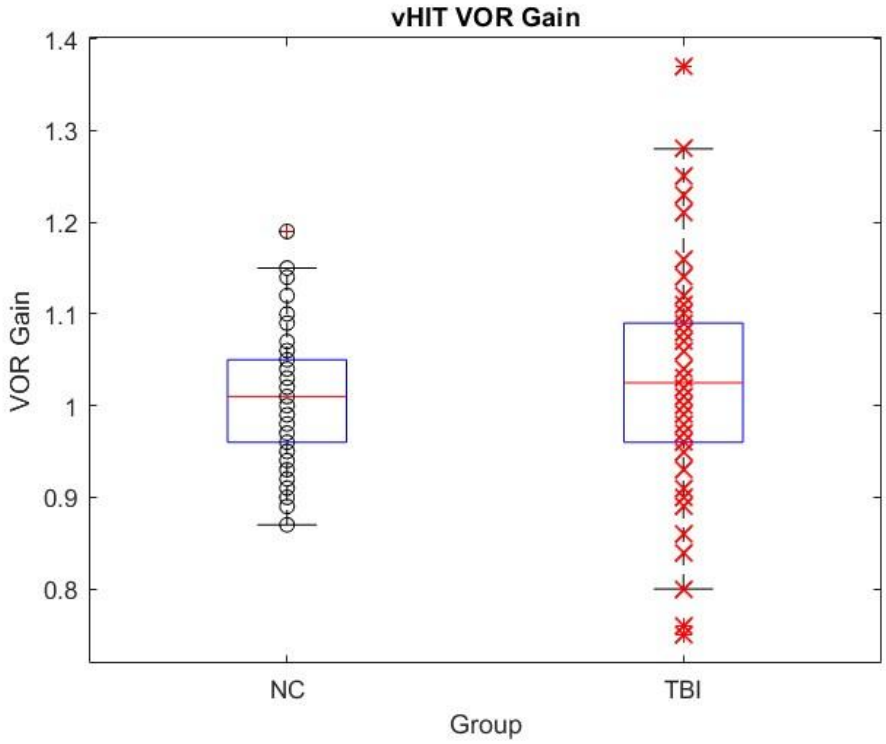

Figure 3.7. vHIT VOR gain as a function of group. VOR gain for each NC participant is denoted by a gray "o", and the VOR gain for each participant with TBI is denoted by a red "x." Boxplots show the median and second and third quartiles.

3.3.2.4 Individual participant results

Response type for each vestibular test was tabulated for each individual participant with TBI (Table 3.4). Overall, only 37% (11/30) of the participants with TBI had normal responses for all three vestibular tests (oVEMP, cVEMP, and vHIT), and 63% (19/30) of TBI participants had abnormal responses for at least one test. Results showed that 33% (10/30) of participants with TBI had abnormal responses for both oVEMPs and cVEMPs, 17% (5/30) had abnormal oVEMP responses but normal cVEMP responses, and 13% (4/30) had abnormal cVEMP responses but normal oVEMP responses. None of the participants with TBI had isolated abnormal vHIT responses. One of the three participants with TBI with an abnormal vHIT response had abnormalities on all three tests. The second participant with TBI and

abnormal vHIT responses also had an abnormal cVEMP response; the third participant with TBI and an abnormal vHIT response also had an abnormal oVEMP response.

TABLE 3.4. Response categories for all vestibular tests for each participant with TBI.

Participant	cVEMP		oVEMP		vHIT	
	Left	Right	Left	Right	Left	Right
1	Normal	Normal	Normal	Normal	Normal	Normal
2	Absent	Normal	Absent	Normal	Normal	Normal
3	Normal	Normal	Normal	Normal	Normal	Normal
4	Amplitude Asymmetry (R > L)		Absent	Normal	Normal	Normal
5	Normal	Normal	Normal	Normal	Normal	Normal
6	Normal	Normal	Amplitude Asymmetry (R > L)		Abnormal	Normal
7	Normal	Normal	Normal	Normal	Normal	Normal
8	Normal	Absent	Normal	Normal	Abnormal	Abnormal
9	Normal	Normal	Normal	Normal	Normal	Normal
10	Normal	Normal	Normal	Normal	Normal	Normal
11	Normal	Normal	Absent	Normal	Normal	Normal
12	Amplitude Asymmetry (L > R)		Normal	Absent	Normal	Normal
13	Amplitude Asymmetry (L > R)		Absent	Absent	Normal	Normal
14	Normal	Normal	Absent	Normal	Normal	Normal
15	Amplitude Asymmetry (L > R)		Normal	Normal	Normal	Normal
16	Amplitude Asymmetry (L > R)		Normal	Normal	Normal	Normal
17	Normal	Normal	Normal	Absent	Normal	Normal
18	Normal	Normal	Normal	Normal	Normal	Normal
19	Amplitude Asymmetry (L > R)		Normal	Absent	Normal	Normal
20	Amplitude Asymmetry (L > R)		Amplitude Asymmetry (L > R)		Abnormal	Abnormal
21	Normal	Normal	Absent	Absent	Normal	Normal
22	Amplitude Asymmetry (R > L)		Normal	Normal	Normal	Normal
23	Normal	Absent	Normal	Absent	Normal	Normal
24	Amplitude Asymmetry (R > L)		Amplitude Asymmetry (R > L)		Normal	Normal
25	Amplitude Asymmetry (L > R)		Amplitude Asymmetry (L > R)		Normal	Normal
26	Normal	Absent	Absent	Absent	Normal	Normal
27	Normal	Normal	Normal	Normal	Normal	Normal
28	Normal	Normal	Normal	Normal	Normal	Normal
29	Normal	Normal	Normal	Normal	Normal	Normal
30	Normal	Normal	Normal	Normal	Normal	Normal

Note: response types are denoted by the following colors: absent = purple, amplitude asymmetry = green, normal = black, abnormal vHIT = red (L > R) indicates the amplitude of the left ear response was greater than the amplitude of the right ear response; (R > L) indicates the amplitude of the right ear response was greater than the amplitude of the left ear response.

3.4 Discussion

The purpose of the study was to determine the prevalence of peripheral vestibular impairment in a sample of adults with chronic moderate-severe TBI. Assessment of peripheral vestibular function using VEMP testing and vHIT showed that 63% of participants with TBI in this study had abnormal cVEMP, oVEMP, VOR gain, or a combination thereof when compared to NC participants. Most impairments were found in the pathways originating from the otolith organs, with an almost equal proportion of impairments affecting the utricular and saccular pathways. These results suggest a greater prevalence and vulnerability of otolith organ pathways, compared to the hSCC pathway, in moderate-severe TBI. Additionally, up to 80% of participants with TBI in this study reported active symptoms that could be vestibular in origin, and up to 36% reported that these symptoms affected their quality of life.

3.4.1 Otolith organ pathway impairments are more prevalent than hSCC VOR pathway impairments in adults with chronic moderate-severe TBI.

Abnormalities in vestibular testing revealed that most impairments were found for measures of otolith organ pathway function rather than for hSCC pathway function (Table 3.4). The group of TBI participants showed evidence of decreased otolith organ pathway function relative to the group of NC participants, with statistically significant group differences for cVEMP corrected amplitude asymmetry and oVEMP amplitude asymmetry. Half (50%) of participants with TBI had absent or asymmetric oVEMP responses, and almost half (47%) of participants with TBI had absent or asymmetric cVEMP responses. This is a higher prevalence of oVEMP and cVEMP abnormalities than those found for adults with mild TBI (Akin et al., 2022; Ernst et al., 2005; Taylor, Wise, Taylor, Chaudhary, & Thorne, 2022), as well as a higher prevalence of cVEMP abnormalities than that shown in adults with sports-related concussions (Gard et al., 2022). This finding could suggest that TBI severity is positively correlated with probability of otolith organ pathway impairment.

Our results are especially interesting when compared to a recent prospective study focused on chronic mild TBI. In this study, only 18% of participants with chronic mild TBI had oVEMP

abnormalities, and only 25% had cVEMP abnormalities (Akin et al., 2022). Similar to our study (Table 2), Akin et. al. (2022) found statistically significant group differences (NC vs. TBI) for cVEMP amplitude asymmetry and found no statistically significant group effects for cVEMP amplitude, cVEMP latency, oVEMP amplitude, or oVEMP latency. However, our study found statistically significant group differences in oVEMP amplitude asymmetry, whereas Akin et. al. (2022) did not. The statistically significant group differences in oVEMP amplitude asymmetry found in our study may further suggest that the prevalence of otolith organ pathway impairment increases as a function of TBI severity.

To the contrary, VOR gain of the hSCCs did not significantly differ between NC and TBI participant groups. Only about 10% of participants with chronic moderate-severe TBI had abnormal VOR gain with the presence of corrective saccades when tested with vHIT in the horizontal plane. The lower occurrence of hSCC VOR impairments compared to otolith organ impairments suggests that the VOR pathway originating from the hSCCs may be less susceptible to the pathophysiological mechanisms of brain injury, even with moderate-severe injuries. This claim would be consistent with prior literature focused on mild TBI, which also highlights a greater prevalence of otolith organ impairments compared to hSCC impairments (Akin & Murnane, 2011; Akin et al., 2017, 2022). It is possible that mechanical trauma that caused brain injury in this study's participants with TBI may have increased the risk of damage to the otolith organs, which are thought to be more vulnerable to trauma compared to the semicircular canals (Park, Lee, Oh, Park, & Suh, 2019). However, our findings are inconsistent with those of Taylor et al. (2022), who showed a greater prevalence of hSCC pathway impairments than otolith organ pathway impairments. This difference could be due to several factors, including the retrospective nature of the Taylor et al. (2022) study, in which differences across clinics and experimenters could have affected the results.

Our results suggest that adults with chronic moderate-severe TBI may have a similar risk for hSCC pathway damage as those with chronic mild TBI. For instance, in the population of participants with chronic mild TBI in the study by Akin et al. (2022), between 6% and 8% showed evidence of hSCC pathway impairment. One caveat is that we tested hSCC pathway function using vHIT, which measures

high-frequency VOR function at head movement frequencies >1Hz, whereas Akin et al. (2022) tested hSCC function using caloric and rotational testing, which measure low- and mid-frequency VOR function at frequencies of 0.003 and 0.01 to 0.64Hz, respectively. Caloric testing is considered the gold standard test of diagnosing peripheral vestibular impairment and, therefore, it is possible that some peripheral impairments were missed in this study by using only vHIT (McCaslin, Jacobson, Bennett, Gruenwald, & Green, 2014). For example, Taylor et al. (2022) showed that 11% of hSCC impairments in participants with chronic mild TBI were found with caloric testing that were not found with vHIT. In that study, a combination of caloric and vHIT results showed that 18% of participants with chronic mild TBI had hSCC pathway impairments. However, based on our clinical experience, vHIT is often thought to be more tolerable for individuals, especially those with TBI. A second prospective study that utilized vHIT to examine hSCC and vertical SCC pathway function showed that 52% of adults with sports-related concussions and chronic dizziness symptoms had abnormal vHIT compared to 0% of non-injured comparison participants (Gard et al., 2022). However, horizontal and vertical SCC pathway abnormalities were combined in the 52% total, making it difficult to compare hSCC pathway abnormalities found in that study to those shown here.

3.4.2 Adults with chronic moderate-severe TBI report active symptoms of dizziness and imbalance that affect their quality of life.

Most (80%) of the participants with TBI self-reported dizziness and almost half (43%) had self-reported imbalance, indicating dizziness and imbalance symptoms may affect a large portion of individuals with chronic moderate-severe TBI. This is higher than the 37-47% of individuals with chronic moderate TBI who reported dizziness and/or vertigo symptoms in previous studies (for review, see Maskell et al., 2006). However, the patients from these studies were diagnosed with moderate TBI decades before the current TBI severity criteria provided by the Mayo Classification System existed. For example, in the study in which 37% of patients reported dizziness, patients were classified as moderate based solely on their GCS score, which was <8 in the first 24 hours (Masson et al., 1996). In the study in

which 47% of patients reported dizziness, patients were classified as moderate based solely on their PTA duration, which was between 1 and 24 hours (Berman & Fredrickson, 1978). Comparatively, the GCS and PTA requirements for individuals with moderate-severe TBI in our study were a GCS of <13 in the first 24 hours and/or a PTA >24 hours, while also considering presence of loss of consciousness and neuroimaging findings. A motivation for the development of the Mayo Classification System was to move beyond grading TBI severity according to single indicators like GCS and PTA alone as each can be influenced by factors unrelated or indirectly related to TBI severity (Malec et al., 2007). Our results suggest that based on current criteria for TBI severity classification, dizziness symptoms may affect a much larger percentage of individuals with chronic moderate TBI than was originally thought.

More than a third of the participants with TBI (36%) had DHI scores indicative of dizziness handicaps (ranging from mild to severe), and almost a third (30%) had ABC scale scores indicative of low-to-moderate level balance functioning, suggesting dizziness and imbalance affect quality of life in individuals with chronic moderate-severe TBI. The mean ABC scale score for the TBI group was 79.8, which was consistent with previous studies of vestibular assessment of adults with TBI (Hays et al., 2019; Kontos et al., 2018; Scherer et al., 2011). The mean DHI score for the TBI group was 17.7, which was consistent with DHI scores reported in some studies of TBI (Joseph et al., 2021; Kontos et al., 2018; Row et al., 2019), but was much lower than DHI scores reported in other TBI studies (Akin et al., 2022; Basford et al., 2003; D'Silva, Chalise, Obaidat, Rippee, & Devos, 2021; Kaufman et al., 2006; Lin et al., 2015; H. P. Ma, Ong, Ou, Chiang, & Lian, 2021; Scherer et al., 2011; Skóra, Stańczyk, Pajor, & Jozefowicz-Korczyńska, 2018). Time since injury could explain the variation seen in DHI scores of TBI participants, with those in the acute phase of injury self-reporting more symptoms of dizziness than those in the chronic phase. For example, of the studies with greater mean DHI scores than those reported in this study, one focused on participants in the acute phase, three included participants in the acute and early chronic (<2 years post injury) phases, and four did not specify time since injury. Comparatively, the time since injury for the participants with TBI in this study ranged from 1 to 23 years, with a mean of 5.96 years.

3.4.3 Conclusions

Adults with moderate-severe TBI deep into the chronic phase of injury report symptoms such as dizziness and imbalance, report decreased quality of life related to dizziness and imbalance symptoms, and show objective evidence of peripheral vestibular impairment. Evidence suggests otolith organ pathway impairments are more prevalent than hSCC pathway impairments in adults with chronic moderate-severe TBI. Vestibular testing for adults with chronic TBI who report persistent dizziness and imbalance may serve as a valuable tool to further understand the pathophysiology that results in vestibular impairment following brain injury, as well as guide the treatment and rehabilitation of individuals with TBI.

CHAPTER 4

Is Spatial Special? The Relationship Between Peripheral Vestibular Function and Spatial Memory in Adults with Chronic Moderate-Severe TBI: Preliminary Data

4.1 Introduction

Spatial cognitive function has been suggested as one of the most sensitive indicators of TBI (Skelton et al., 2000). Patients with TBI can have a variety of spatial cognitive impairments, such as deficits in visuospatial organization (J.M. et al., 1997), spatial learning and memory (Lehnung et al., 2001; Skelton et al., 2000, 2006), and spatial reconstruction (Rigon et al., 2020). TBI is also correlated with impairments in navigation and environmental exploration, which requires spatial recognition, memory, and planning (Skelton et al., 2006). Notably, adults with TBI have similar rates of navigation errors in virtual and real environments (Sorita et al., 2013). Recent studies have shown that adults with hippocampal amnesia, common in adults with chronic moderate-severe TBI, have difficulty remembering the locations of as little as three novel objects on a screen, and that their performance on this triplet binding task is significantly poorer than that of non-injured comparison participants (Konkel, Warren, Duff, Tranel, & Cohen, 2008).

Similarly, patients with vestibular dysfunction can also have impairments in spatial cognitive abilities, such as deficits in spatial memory and navigational abilities (Brandt et al., 2005). It is unsurprising that vestibular dysfunction would be correlated with spatial cognitive deficits, given that spatial awareness depends on an individual's ability to perceive where their head and body are in space, and vestibular dysfunction reduces this perception during head movements. However, data suggests that even in the absence of vestibular or somatosensory stimulation (i.e., participants are stationary), intact vestibular function remains critical for spatial navigation (Brandt et al., 2005).

Elucidating the consequences of vestibular injury in adults with TBI is critical to understanding the anatomical and physiological contributions (peripheral vestibular vs. central) to spatial cognitive

deficits in TBI populations. Furthermore, spatial cognition is required for everyday tasks, such as navigating living spaces, driving, and remembering the location of important objects, indicating spatial cognitive deficits may present a significant decrease in quality of life. Therefore, examining whether peripheral vestibular impairment mediates spatial cognitive ability could lead to more successful treatment and rehabilitation options for TBI patients.

The aim of the study in Chapter 4 is to examine whether peripheral vestibular function mediates spatial memory accuracy in adults with chronic moderate-severe TBI, which to date has not been reported in this population. It was hypothesized that a group of participants with TBI and vestibular impairment (TBI-VI) would have the lowest spatial memory accuracy scores, followed by a group of participants with TBI and no vestibular impairment (TBI-No VI) with intermediate spatial memory accuracy scores, and a group of non-injured comparison (NC) participants with the highest spatial memory accuracy scores. It was also hypothesized that there would be statistically significant differences in spatial memory accuracy between all three groups. To control for the possibility that the relationship between subgroup (NC vs. TBI-No VI vs. TBI-VI) and memory extended to additional non-spatial relational memory tasks, temporal memory accuracy scores were also assessed. It was hypothesized that the NC group would have the highest temporal memory accuracy scores, followed by the TBI-No VI and TBI-VI groups with temporal memory scores that were similar to each other but lower than those of the NC group. Finally, it was hypothesized that there would not be statistically significant differences in temporal memory accuracy between the TBI-No VI and TBI-VI groups.

4.2 Methods

4.2.1 Participants

The participants who completed the peripheral vestibular experiments in Chapter 3 were recruited to complete an assessment of spatial and temporal relational memory. A total of 25 NC participants and 24 participants with TBI completed this experiment. All 25 NC participants had normal peripheral

vestibular function, 10 participants with TBI had normal peripheral vestibular function, and 14 participants with TBI had an impairment in at least one peripheral vestibular organ. Peripheral vestibular function was assessed using vestibular evoked myogenic potentials and video head impulse test as described in Chapter 3 (see Table 3.4 for results of each peripheral vestibular test for each participant with TBI).

NC participants ranged in age from 20 to 53 years (mean = 35.0, SD = 8.77), and participants with TBI ranged in age from 24 to 55 years (mean = 37.1, SD = 10.27). Years of completed education for participants in the NC and TBI groups ranged from 12 to 20 (NC: mean = 14.80, SD = 2.38; TBI: mean = 14.92, SD = 2.50). There were no statistically significant differences between the NC and TBI groups for age (z = -0.491, p = 0.624) or years of education (z = -0.207, p = 0.836). Demographic information for the NC and TBI groups is shown in Table 4.1.

TABLE 4.1. Demographic information for NC and TBI groups.

	NC Group (N = 25)				**TBI Group (N = 24)**			
	n (%)	**Mean**	**SD**	**Range**	**n (%)**	**Mean**	**SD**	**Range**
Age (years)		35.0	8.77	20 - 53		37.1	10.27	24 - 55
EDU (years)		14.80	2.38	12 - 20		14.92	2.50	12 - 20
Sex (female)	13 (52)				12 (50)			

Note: EDU, Completed education

Within the TBI group, those with normal peripheral vestibular function (TBI- No VI) and those with peripheral vestibular impairment (TBI- VI) ranged in age from 24 to 55 years (TBI-No VI: mean = 32.7, SD = 8.87; TBI- VI: mean = 40.2, SD = 10.33). Years of completed education for both TBI groups ranged from 12 to 20 (TBI-No VI: mean = 14.40, SD = 2.63; TBI-VI: mean = 15.29, SD = 2.43). There were no statistically significant differences between the TBI-No VI and TBI-VI groups for age (z = -1.760, p = 0.078) or years of education (z = -0.667, p = 0.505). Demographic information for the TBI

groups with and without peripheral vestibular impairment is shown in Table 4.2.

TABLE 4.2. Demographic information for TBI groups with and without vestibular impairment.

	TBI- No VI Group (N = 10)				TBI- VI Group (N = 14)			
	n (%)	**Mean**	**SD**	**Range**	**n (%)**	**Mean**	**SD**	**Range**
Age (years)		32.7	8.87	24 - 55		40.2	10.33	24 - 55
EDU (years)		14.40	2.63	12 - 20		15.29	2.43	12 - 20
Sex (female)	4 (40)				8 (57)			

Note: VI, Vestibular impairment; EDU, Completed education

4.2.2 Triplet binding task (TBT)

To assess spatial and temporal memory, all participants completed a triplet binding task (TBT), a task that assesses relational memory (Konkel et al., 2008; Lee et al., 2020; Lee, Wendelken, Bunge, & Ghetti, 2016). The task was completed in one session and monitored by an experimenter either virtually via Zoom or in-person in the laboratory. Participants were asked to study a group of three abstract color images likely to be novel to the participants and void of typical semantic cues. Participants completed two testing blocks, assessing either item-space or item-time, representing spatial and temporal memory, as described below. The order of blocks was randomized across participants, and each block consisted of five encoding-retrieval phases.

The encoding phase preceded each retrieval phase and consisted of a set of three novel objects. For each encoding trial, each of the three objects was presented for one second to a specific location on the computer screen (either top-left, bottom-center, or top right). Items in a triplet were presented sequentially in a separate location on the screen (one in top-left, one in top-right, and one in bottom-center). This was followed by a one-second intertrial interval in which the participants were asked to fixate on a center cross. Two more trials and intertrial intervals immediately followed. This encoding phase was then repeated a second time, with three additional trials.

The retrieval phase immediately followed each encoding phase and consisted of 15 target and 15

lure probes. Whether a target or lure probe was used depended on the testing block being assessed. For the item-space block trials, three objects from the same encoding trial appeared simultaneously in three different spatial locations on the computer screen. Participants were asked to indicate whether all three objects were located in their original positions. In target trials, all objects were positioned in their original spatial locations; in lure trials, the spatial positions of two objects were switched. Items switched in lure trials were randomized. This condition did not require temporal retrieval cues. For the item-time block trials, three objects from the same encoding trial appeared one at a time on the center of the screen (not in original spatial positions). Participants were asked to indicate whether the objects occurred in the same sequence as they appeared during the encoding trial. In target trials, all objects were presented in the original sequence; in lure trials, the order of two objects was switched. Items switched in lure trials were randomized. This condition did not require spatial retrieval cues.

4.2.3 Analysis

Accuracy scores, represented by d', for each testing block were computed as the difference between hit and false alarm rates across the 15 trials. Hit rates were calculated as the proportion of correct responses during target trials (i.e., the participant responded "correct" when the correct position or sequence of objects was *correct*). False alarm rates were calculated as the proportion of incorrect responses during lure trials (i.e., the participant responded "correct" when the correct position or sequence of objects was *incorrect*).

4.2.4 Statistical analysis

MATLAB version R2023a was used for all statistical analysis. Descriptive statistics were calculated to determine the mean and standard deviation for the NC, TBI-No VI, and TBI-VI groups for age, years of education, spatial memory accuracy (d'), and temporal memory accuracy (d'). Kruskal Wallis tests (kruskalwallis function in MATLAB) were used to determine whether spatial and temporal memory accuracy scores from the NC, TBI-No VI, and TBI-VI groups came from the same distribution

or whether there were there were statistically significant differences between at least two groups. For cases in which the null hypothesis was rejected in the Kruskal Wallis test, post hoc Dunn's test with Bonferroni correction was used to determine which pairwise group differences were statistically significant. Finally, spearman correlation was used to test whether spatial memory accuracy score was significantly correlated with cVEMP and oVEMP amplitude asymmetry described in Chapter 3. An alpha level of 0.05 was used to determine significance for all statistical tests.

4.3 Results

Spatial memory accuracy was assessed using a triplet binding task (TBT), which was completed by NC, TBI-No VI, and TBI-VI groups. Figure 4.1 shows the spatial memory accuracy scores (d') for all participants. For the NC group, spatial memory accuracy scores ranged from 0.76 to 3.46 (mean = 2.38, SD = 0.78). For the TBI-No VI group, spatial memory accuracy scores ranged from 0.86 to 4.07 (mean = 2.13, SD = 1.02). For the TBI-VI group, spatial memory accuracy scores ranged from 0.11 to 3.77 (mean = 1.53, SD = 0.99). This suggests that, overall, the NC group performed the item-space TBT task better than the TBI-No VI group, and the NC and TBI-No VI groups performed the item-space TBT task better than the TBI-VI group. Kruskal Wallis analysis revealed that spatial memory accuracy scores from the NC, TBI-No VI, and TBI-VI did not come from the same distribution, with statistically significant mean spatial memory accuracy scores between at least two groups ($F(2, 46) = 8.014$, $p = 0.018$). Dunn's post-hoc analysis with Bonferroni correction revealed statistically significant differences in spatial memory accuracy scores between the NC and TBI-VI groups ($p = 0.014$), but no statistically significant differences in spatial memory accuracy between the NC and TBI-No VI groups ($p = 0.986$) or between the TBI-No VI and TBI-VI groups ($p = 0.486$).

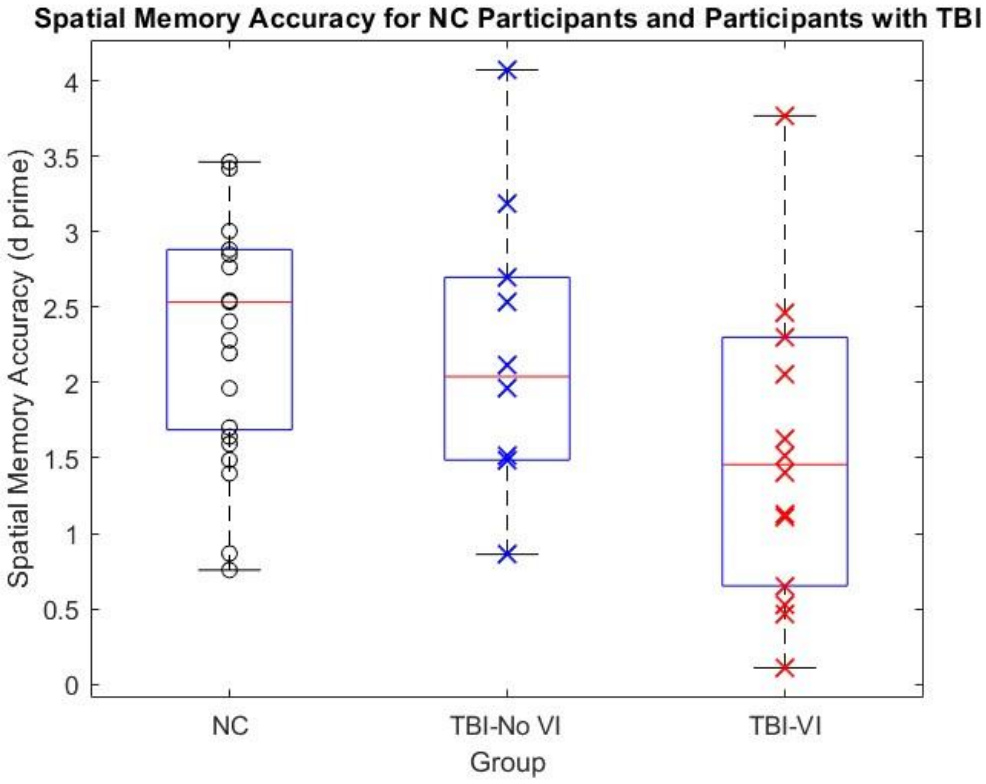

Figure 4.1. Spatial memory accuracy scores (d') for NC participants (black circles), participants with TBI-No VI (blue x's), and participants with TBI and VI (red x's).

To determine whether group differences were exclusive to spatial memory or were generalized to an additional relational memory task, temporal memory was assessed using the TBT. Figure 4.2 shows the temporal memory accuracy scores (d') for all participants. For the NC group, temporal memory accuracy scores ranged from 0.87 to 3.77 (mean = 2.66, SD = 0.95). For the TBI-No VI group, temporal memory accuracy scores ranged from 0.11 to 4.07 (mean = 2.26, SD = 1.55). For the TBI-VI group, temporal memory accuracy scores ranged from 0.54 to 3.77 (mean = 2.07, SD = 1.04). This suggests that, overall, the NC group performed the item-time TBT task better than the TBI-No VI group, and the NC and TBI-No VI groups performed the item-time TBT task better than the TBI-VI group. Kruskal Wallis analysis revealed that temporal memory accuracy scores from the NC, TBI-No VI, and TBI-VI came from the same distribution, with no statistically significant mean temporal memory accuracy scores

between any group pairs ($F(2, 46) = 2.443$, $p = 0.295$).

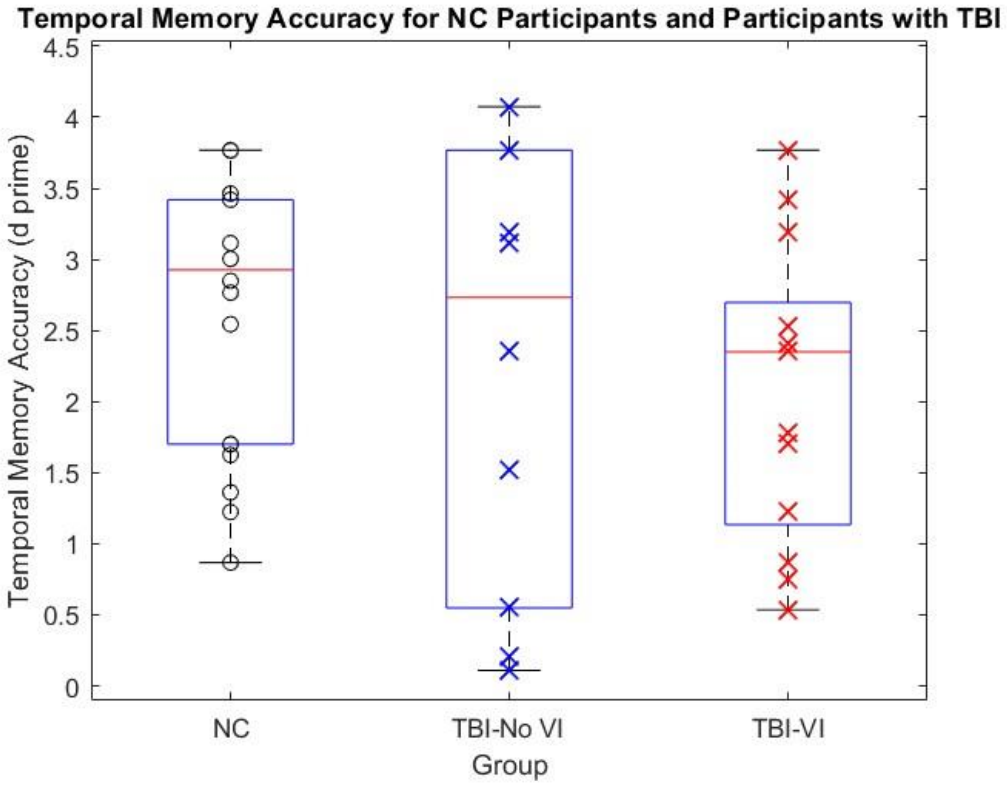

Figure 4.2. Temporal memory accuracy scores (d') for NC participants (black circles), participants with TBI-No VI (blue x's), and participants with TBI and VI (red x's).

Since statistically significant differences in spatial memory accuracy scores were found between the NC and TBI-VI groups, correlations between spatial memory accuracy and objective measures of peripheral vestibular function were explored. All participants in the TBI-VI group had at least one otolith organ pathway impairment as evidenced by abnormal VEMP responses found in Chapter 3. Therefore, correlations between spatial memory accuracy and cVEMP/oVEMP amplitude asymmetry were investigated in individuals with present VEMP responses. Figure 4.3 shows the relationship between spatial memory accuracy and cVEMP amplitude asymmetry for all participants. A statistically significant negative relationship between spatial memory accuracy and cVEMP amplitude asymmetry was found (r =

-0.302, p = 0.039), indicating larger cVEMP amplitude asymmetries resulted in significantly lower spatial memory accuracy overall.

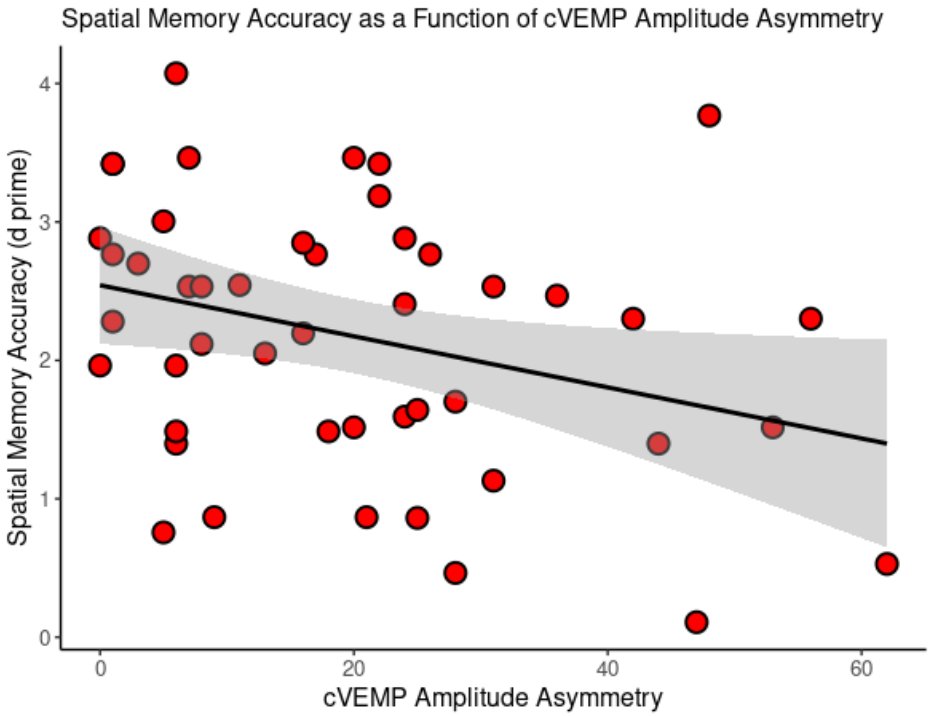

Figure 4.3. Spatial memory accuracy scores (d') as a function of cVEMP amplitude asymmetry (%) for all participants (red circles).

Figure 4.4 shows the relationship between spatial memory accuracy and oVEMP amplitude asymmetry for all participants. While a negative relationship was found, indicating larger oVEMP amplitude asymmetries resulted in lower spatial memory accuracy overall, this relationship was not statistically significant (r = -0.230, p = 0.143).

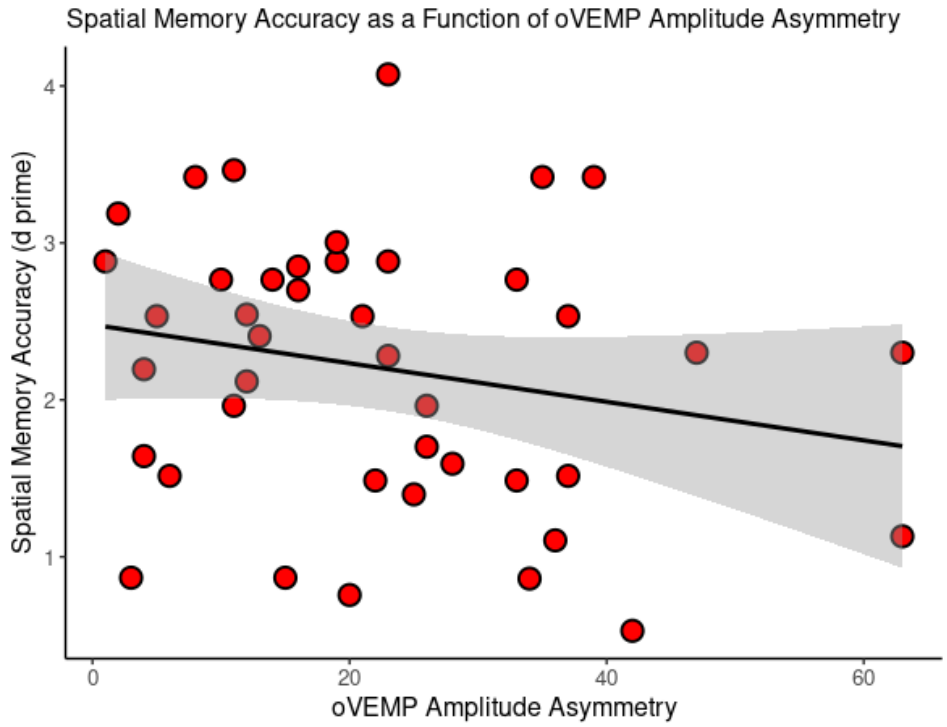

Figure 4.4. Spatial memory accuracy scores (d') as a function of oVEMP amplitude asymmetry (%) for all participants (red circles).

4.4 Discussion

4.4.1 Is spatial special? Preliminary results suggest spatial memory may be selectively affected by the combination of TBI and peripheral vestibular impairment.

The aim of this preliminary report was to determine whether there is a relationship between peripheral vestibular function and spatial memory ability in adults with chronic moderate-severe TBI. The TBT allowed us to 1) determine spatial memory accuracy, and 2) examine temporal memory accuracy to control for the possibility that the relationship between subgroup (NC vs. TBI-No VI vs. TBI-VI) and memory extends to additional non-spatial relational memory tasks. Preliminary results support our hypothesis that the NC group has the highest spatial memory accuracy scores, followed by the TBI-No VI group with lower spatial memory accuracy scores, and the TBI-VI group with the lowest spatial memory accuracy scores. Although there were no statistically significant differences in spatial memory accuracy

between the NC and TBI-No VI groups or between the TBI-No VI and TBI-VI groups, our hypothesis that there are statistically significant differences in spatial memory accuracy between the NC and TBI-VI groups was supported. This suggests spatial memory may be impeded by the combination of TBI and peripheral vestibular impairment.

Preliminary results also support our hypothesis that the NC group has higher average temporal memory scores than the TBI-No VI and TBI-VI groups. However, our hypothesis that the NC group would have statistically significant differences in temporal memory accuracy than the TBI-No VI and TBI-VI groups was not supported. A similar pattern for spatial memory was found for temporal memory, with the highest temporal memory accuracy scores found for the NC group, followed by the TBI-No VI group with lower temporal memory accuracy scores, and the TBI-VI group with the lowest temporal memory accuracy scores. However, there were no statistically significant differences in temporal memory accuracy scores between any of the groups. This suggests temporal memory was not affected by the combination of TBI and peripheral vestibular impairment in this participant population.

It is unsurprising that the NC group had significantly higher spatial memory accuracy than the TBI-VI group. Both TBI and vestibular impairment have been shown to separately affect spatial cognitive ability (Brandt et al., 2005; Lehnung et al., 2003; Rigon et al., 2020; Skelton et al., 2006), and anatomical connections between structures implicated in memory and vestibular function suggest both systems may contribute to spatial cognition (Hitier et al., 2014; Smith, 1997). What is more surprising is that the NC group did not have significantly higher spatial memory accuracy than the TBI-No VI group or significantly higher temporal memory accuracy than either of the TBI groups. It is known that adults with moderate-severe TBI have difficulties with multiple aspects of memory (for review, see Vakil, 2005), including spatial (Lehnung et al., 2001; Rigon et al., 2020; Skelton et al., 2000, 2006; Sorita et al., 2013) and temporal memory (for review, see Mioni, Grondin, & Stablum, 2014), relative to non-injured individuals.

There is more than one explanation for the lack of statistically significant differences in spatial memory between the NC and TBI-No VI groups and in temporal memory between the NC and both TBI

groups. First, it is possible that the population of participants with TBI who completed this study are not representative of the population of individuals with chronic moderate-severe TBI. TBI is a diffuse disorder even within the chronic phase and moderate-severe categories. Other variables such as the mechanism of injury and/or location of injury likely play a large role in relational memory abilities. For example, it is known that adults with hippocampal amnesia perform poorly in both the item-space and item-time TBT tasks (Konkel et al., 2008). Second, it is possible that including larger sample sizes in each group would reveal more robust statistically significant group differences in spatial memory accuracy scores but not temporal memory accuracy scores.

4.4.2 Spatial memory accuracy is significantly correlated with at least one objective measure of peripheral vestibular impairment.

Since all participants in the TBI-VI group had evidence of at least one impairment of the otolith organ pathways, we explored the relationship between spatial memory accuracy and VEMP responses, which are objective measures of otolith organ pathway function. When correlations between spatial memory accuracy and cVEMP amplitude asymmetry were investigated, a statistically significant negative relationship was found, indicating larger cVEMP amplitude asymmetries resulted in significantly lower spatial memory accuracy overall. Because cVEMPs measure the response of the saccular pathway, this result suggests saccular pathway function significantly affects spatial memory ability. When correlations between spatial memory accuracy and oVEMP amplitude asymmetry were investigated, a negative relationship was found, indicating larger oVEMP amplitude asymmetries resulted in significantly lower spatial memory accuracy overall; however, this relationship was not statistically significant. Because oVEMPs measure the response of the utricular pathway, this result suggests utricular pathway function may affect spatial memory ability, although this should be explored further.

One possible reason a statistically significant correlation between spatial memory accuracy and oVEMP amplitude asymmetry was not found is that absent VEMP responses were not accounted for in the data. While 96% (47/49) of participants who completed the TBT had present cVEMP responses, only

86% (42/49) had present oVEMP responses to be included in correlational analysis. As explained in Chapter 3, absent VEMP responses equate to peripheral vestibular impairment, indicating some information about the relationship between spatial memory and VEMP response is lost with this correlational analysis.

It is unsurprising that spatial memory accuracy is correlated with otolith organ function, given the increasing evidence suggesting otolith organ-driven effects on spatial memory (for review, see Smith, 2019). For example, compared to control mice, a mouse model of otolith loss shows several deficits in spatial memory, including spontaneous alternation in the Y test (Machado et al., 2012), longer durations in the place recognition test (Machado et al., 2012), impaired homing ability (Blankenship et al., 2017; Yoder et al., 2015), and lower percentages of correct choices and worse improvement in the radial arm maze (Yoder & Kirby, 2014). Importantly, the mice with otolith loss in one study were shown to have impaired spatial memory but no significant impairments in non-spatial memory tasks (Machado et al., 2012).

Evidence from studies of human populations also suggests an association between otolith organ function and spatial cognition (for review, see Smith, 2019). Notably, this relationship has been shown in populations of patients with cognitive disorders, such as mild cognitive impairment (MCI) and Alzheimer's Disease (AD). For example, patients with a cognitive disorder who show spatial cognitive impairments have a significantly greater prevalence of peripheral vestibular loss (Wei, Oh, Harun, Ehrenburg, & Agrawal, 2018b). Compared to participants with MCI or AD and no peripheral vestibular impairment, participants with MCI or AD and saccular impairment, as measured using cVEMPs, perform significantly more errors on the Money Road Map Test (Wei et al., 2018b). Participants with MCI or AD and bilateral saccular impairment also have significantly greater difficulty with driving, compared to those with MCI or AD and no saccular impairment, which may be related to decreased spatial cognitive ability (Wei, Oh, Harun, Ehrenburg, & Agrawal, 2018a). Overall, studies show that having an abnormal cVEMP response is associated with a 3- to 5-fold increase in the probability of having MCI or AD (Harun, Oh, Bigelow, Studenski, & Agrawal, 2016; Wei et al., 2019), and an abnormal oVEMP response

is associated with a 4-fold increase in the probability of having MCI or AD (Wei et al., 2019). Importantly, the same study showed that the odds of having a cognitive disorder were not significantly associated with VOR gain measured from the semicircular canal pathways (Wei et al., 2019). Furthermore, it was found that decreased cVEMP amplitude is significantly correlated with lower average hippocampal volume (Kamil, Jacob, Ratnanather, Resnick, & Agrawal, 2018), which is consistent with a previous study showing a 17% decrease in hippocampal volume in people with vestibular loss, relative to non-injured comparison participants (Brandt et al., 2005).

4.4.3 Conclusions

Preliminary data suggest that relative to demographically matched non-injured comparison participants, there is a significant decrease in spatial memory ability in adults with chronic moderate-severe TBI and peripheral vestibular impairment, specifically otolith organ impairment. However, this difference does not extend to temporal memory, suggesting spatial memory may be selectively impaired in individuals with combined TBI and peripheral vestibular impairment. Preliminary results also show a significant negative relationship between spatial memory accuracy and cVEMP amplitude asymmetry, suggesting saccular pathway impairment is associated with lower spatial memory ability. Although spatial memory accuracy did not significantly correlate with oVEMP amplitude asymmetry, caveats, such as small sample size and the exclusion of absent responses in analysis, need to be considered. Overall, our results validate the need for further exploration of the relationship between peripheral vestibular function and spatial memory in adults with chronic moderate-severe TBI. Examining this relationship could lead to more successful treatment and rehabilitation options for TBI patients, including the use of vestibular rehabilitation training and/or specialized cognitive training.

CHAPTER 5

Current Knowledge and Future Directions Concerning Peripheral Vestibular Function and Spatial Memory in Adults with Chronic Moderate-Severe TBI

Traumatic Brain Injury (TBI) is a significant public health concern with an estimated 50-60 million new TBI cases annually worldwide (Maas et al., 2017). Symptoms such as dizziness and/or vertigo are commonly reported by patients with TBI (Maskell et al., 2006) and may be induced by damage to the vestibular pathway, including the semicircular canals and otolith organs of the inner ear (for review, see Šarkić et al., 2021). However, little is known about peripheral vestibular function in adults with chronic moderate-severe TBI. Furthermore, several lines of evidence show anatomical connections between the vestibular system and brain areas involved in spatial cognition (e.g., hippocampus; for review, see Hitier et al., 2014; Smith, 1997). It is also known that TBI and vestibular damage can cause hippocampal atrophy and spatial cognitive impairment (Brandt et al., 2005; Lehnung et al., 2003; Rigon et al., 2020; Skelton et al., 2006; Tomaiuolo et al., 2004). However, it is unclear what influence peripheral vestibular impairments have on spatial cognitive deficits commonly observed in adults with TBI. Therefore, the aim of this dissertation was threefold: to assess the 1) prevalence of vestibular symptoms, 2) prevalence of peripheral vestibular impairment, and 3) correlation between peripheral vestibular function and spatial cognition, in adults with chronic moderate-severe TBI.

5.1 Summary of findings

5.1.1 Adults with chronic moderate-severe TBI report active symptoms of dizziness and imbalance that affect their quality of life.

Assessment using a standard case history form showed that most (80%) of the participants with TBI self-reported dizziness and almost half (43%) had self-reported imbalance, indicating dizziness and

imbalance symptoms may affect a large portion of individuals with chronic moderate-severe TBI. Furthermore, more than a third of the participants with TBI (36%) had Dizziness Handicap Inventory (DHI) scores indicative of dizziness handicaps (ranging from mild to severe), and almost a third (30%) had Activities-specific Balance Confidence (ABC) scale scores indicative of low-to-moderate level balance functioning, suggesting dizziness and imbalance affect quality of life in individuals with chronic moderate-severe TBI. These results suggest dizziness and imbalance may affect a much larger percentage of individuals with chronic moderate-severe TBI than was originally thought.

5.1.2 Adults with chronic moderate-severe TBI show evidence of peripheral vestibular impairment.

Assessment of peripheral vestibular function using vestibular evoked myogenic potential (VEMP) testing and video head impulse test (vHIT) showed that 63% of participants with TBI in had abnormal cVEMP, oVEMP, VOR gain, or a combination thereof, compared to only 7% of NC participants. Most impairments were found in the pathways originating from the otolith organs, with an almost equal proportion of impairments affecting the saccular and utricular pathways. These results suggest a greater prevalence and vulnerability of otolith organ pathways, compared to the hSCC pathway, in chronic moderate-severe TBI. These results suggest peripheral vestibular testing for adults with chronic moderate-severe TBI who report persistent dizziness and imbalance may serve as a valuable tool to further understand the pathophysiology of their symptoms, as well as guide the treatment and rehabilitation of individuals with TBI, especially those classified as chronic moderate-severe.

5.1.3 Peripheral vestibular impairment may affect spatial memory in adults with chronic moderate-severe TBI.

Performance on a triplet binding task (TBT) showed that the group of participants with TBI had lower average spatial memory accuracy scores compared to the NC group. Furthermore, the subgroup of participants with TBI and peripheral vestibular impairment (TBI-VI) had lower average spatial memory scores than the subgroup of participants with TBI and no peripheral vestibular impairment (TBI-No VI).

This suggests peripheral vestibular impairment may affect spatial memory ability in adults with chronic moderate-severe TBI. Although the TBI-VI group also had lower average temporal memory accuracy scores than the TBI-No VI, the group differences in temporal memory accuracy were much smaller than those of spatial memory accuracy and may be indicative of other differences across groups (e.g., mechanism of injury, hippocampal aphasia). Overall, our results validate the need for further exploration of the relationship between peripheral vestibular function and spatial memory in adults with chronic moderate-severe TBI. Examining this relationship could lead to more successful treatment and rehabilitation options for patients with TBI, including the use of specialized cognitive training.

5.2 Limitations

5.2.1 Limitations of Chapter 3

This study of peripheral vestibular function in adults with chronic moderate-severe TBI has limitations that should be considered. First, hSCC pathway function was tested using vHIT, which measures VOR function for natural (high frequency) head movement frequencies of about 1-5 Hz. As previously mentioned, the gold standard test for diagnosing peripheral SCC function is caloric testing (low frequency), which was not included in this study. It is possible that some hSCC pathway impairments were missed in our TBI population due to the lower sensitivity of vHIT compared with other tests of hSCC pathway function.

Second, VEMP responses elicited by air-conducted stimuli can be absent in individuals with conductive hearing loss, which would presumably be caused by middle ear, and not otolith organ (vestibular), impairment. Although we recorded normal tympanometry for participants with absent VEMP responses, we did not assess pure tone air and bone conduction thresholds in these participants and cannot completely rule out conductive hearing loss. However, there is evidence that the prevalence of conductive hearing loss in individuals with non-blast related, mild TBI is relatively uncommon (Lew, Jerger, Guillory, & Henry, 2007; Oleksiak, Smith, St. Andre, Caughlan, & Steiner, 2012). Both reports

investigated hearing loss in veterans and found that sensorineural hearing loss, which does not impact VEMP response rates, was the most common type of hearing loss following non-blast TBI. Lew et al. reported that only 3.7% (4/108) of participants had conductive hearing loss, while Oleksiak et al. reported that only 5.41% (2/37) had conductive hearing loss. Tympanometry and otoscopy, which were completed in this study, should have identified some potential causes of conductive hearing loss (e.g., middle ear effusion, tympanic membrane perforation, ossicular discontinuity or fixation, etc.) in our participants. Based on the published data, we would expect that the prevalence of any other confounding conductive hearing loss effects, if present, should have been low.

Additionally, it is unclear whether the impairments found in this study were physiologically or functionally compensated. Therefore, it is difficult to fully understand how impairments observed in this study were actively contributing to gaze and postural stability in the TBI group. Tests of functional balance may have provided more information about vestibular function in our participants with TBI. For example, a previous study of chronic mild TBI showed a significant effect of group (NC vs. TBI) on SOT composite equilibrium score (CES; Akin et al., 2022). It is also likely that peripheral impairments alone would not fully explain the amount of dizziness and imbalance experienced in our TBI group.

5.2.2 Limitations of Chapter 4

As this study included preliminary analysis of the relationship between peripheral vestibular function and spatial memory in adults with chronic moderate-severe TBI, some limitations should be considered. First, this study included a subsample of participants with TBI and demographically matched NC participants from Chapter 3. The NC group consisted of 25 participants, while the TBI-No VI group included only 10 participants, and the TBI-VI groups included only 14 participants. With small and unequal sample sizes across groups, it is difficult to complete more complex statistical analysis and make meaningful inferences about the average memory accuracy scores across groups.

Additionally, the TBT assesses a specific form of spatial cognition, the ability to remember the locations of three novel abstract stimuli on a computer screen. It is possible that assessing a different form

of spatial cognition would elicit more robust differences between groups, and especially between the TBI-No VI and TBI-VI groups. For example, people with vestibular impairment have been shown to have impaired navigational abilities (Brandt et al., 2005), which is also true for individuals with TBI (Skelton et al., 2006; Sorita et al., 2013).

5.3 Future directions

Chapter 3 provides evidence of peripheral vestibular impairment in adults with chronic moderate-severe TBI. However, further prospective studies are needed to provide a more comprehensive picture of peripheral and central vestibular function in this population to further elucidate the origins of active dizziness and imbalance. First, future studies should further examine the prevalence of peripheral vestibular impairments across chronic TBI severity and across acute and chronic phases of moderate-severe TBI. This will help clarify the relationship between peripheral vestibular impairment, TBI phase, and TBI severity. It is likely that the prevalence of otolith organ impairments would remain consistent across acute and chronic phases of TBI, considering damage to otolith organs does not fully resolve (González-Garrido et al., 2021). However, it is unclear whether individuals with TBI centrally compensate for these impairments in the same manner and time course as non-injured individuals.

Additionally, future studies assessing vestibular function in adults with chronic moderate-severe TBI should include additional vestibular measurements. This includes additional tests of vestibular function (e.g., vertical semicircular canal testing using vHIT), functional gaze stabilization tests, and tests of balance to further understand the functional impact of chronic TBI on the integrity of vestibular reflex pathways and processing.

Chapter 4 provides preliminary evidence that suggests peripheral vestibular impairment may affect spatial memory ability in adults with chronic moderate-severe TBI. However, further prospective studies are needed to provide a more comprehensive picture of spatial cognition in adults with TBI and vestibular impairment to further elucidate the relationship between peripheral vestibular impairment and spatial memory in this population. First future studies should use larger sample sizes, especially in both

TBI subgroups. Although statistically significant differences in spatial memory accuracy score were found between the NC and TBI-VI groups, no other statistically significant group differences were found. A power analysis based on the current mean spatial memory accuracy scores and standard deviations for the NC, TBI-No VI and TBI-VI groups revealed that in order to find statistically significant differences in spatial memory accuracy between the NC and TBI-No VI groups with a power of 0.8, a sample size of 79 participants per group would be required; the sample size needed to find statistically significant differences between the TBI-No VI and TBI-VI groups with a power of 0.8 is 25 participants per group. It is possible larger and equal sample sizes across NC, TBI-No VI, and TBI-VI would elicit more robust and statistically significant group differences.

Next, future studies should include additional assessments of spatial cognition, such as navigational abilities, in adults with TBI and vestibular impairment. It is probable that correlations between peripheral vestibular function and spatial navigation would be most apparent in adults with TBI and vestibular impairment (TBI-VI) when a task such as the virtual Morris water maze is used to assess spatial cognition; accuracy in the virtual Morris water maze is impaired in groups of participants with TBI (Skelton et al., 2006) and in those with vestibular impairment (Brandt et al., 2005).

5.4 Clinical implications

The results of this dissertation have several clinical implications. First, adults with TBI, and especially those in the chronic phase of injury, are not routinely referred for vestibular testing. Assessing vestibular function using standard clinical methods may help to elucidate whether peripheral and/or central involvement is contributing to active symptoms of dizziness and imbalance in TBI populations. This could ultimately help direct individuals with TBI to the appropriate medical provider for further assessment and/or treatment. Second, a review of the literature noted that vestibular testing in patients with brain injury is often limited to hSCC pathway VOR function, although VEMP abnormalities have been found to be more prevalent in at least some TBI groups (Akin et al., 2022). The results of Chapter 3 provide further support for the inclusion of VEMP testing in the clinical assessment of TBI patient

populations.

Additionally, the results of this dissertation show a large prevalence of dizziness and imbalance in adults with chronic moderate-severe TBI. Falls are a leading cause of brain injury (Friedland et al., 2014), and falls due to dizziness and imbalance could increase the risk of a second brain injury. Finally, the results of this dissertation have implications for treatment and rehabilitation guidelines for adults with TBI. For example, otolith organ impairments have been related to functional imbalance (Basta, Todt, Scherer, Clarke, & Ernst, 2005) by affecting the vestibulocollic reflex pathway (saccule), the vestibulospinal reflex pathway (saccule), and/or the VOR pathway (utricle) (Uchino & Kushiro, 2011). The results of Chapter 3 further support the inclusion of vestibular rehabilitation to treat symptoms of otolith organ disorders. Curthoys and Manzari suggest that compensation to unilateral otolith organ deficits parallels recovery that is established for semicircular canal impairment (Curthoys & Manzari, 2013). A recent study also showed lower disability and improved quality of life for such individuals after this type of compensation (Sestak, Maslovara, Zubcic, & Vceva, 2020).

5.5 Conclusions

Adults with moderate-severe TBI deep into the chronic phase of injury report vestibular symptoms such as dizziness and imbalance, report decreased quality of life related to dizziness and imbalance symptoms, show objective evidence of peripheral vestibular impairment, and show evidence of spatial memory impairment. Future studies should further examine peripheral and central vestibular impairment and further elucidate whether vestibular impairment exacerbates spatial cognitive impairment in this population. Vestibular testing for adults with chronic TBI who report persistent dizziness and imbalance may serve as a valuable tool to further understand the pathophysiology that results in vestibular impairment following brain injury. Vestibular and cognitive testing, specifically related to spatial cognition, may help guide the treatment and rehabilitation of individuals with TBI.

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