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VESTIBULAR DYSFUNCTION AND BRAIN FOG

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THESIS APPROVAL PAGE

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ABSTRACT

VESTIBULAR DYSFUNCTION AND BRAIN FOG

Maria Makhina, B.A.

Some patients with vestibular loss report experiencing a phenomenon called brain fog. While used relatively common, the exact meaning of the term is still unclear. In this study we attempted to understand the essence of brain fog, its manifestation in patients, and its cofounding factors. Sixty-eight participants with various vestibular diagnoses were recruited through the Johns Hopkins Outpatient Neuro-Otology Center. The participants were divided into two groups, Brain Fog Yes (n = 39) and Brain Fog No (n = 29), based on the presence of brain fog. Both groups partook in a four-part diagnostic questionnaire, consisted of the Patient Health Questionnaire (PHQ-9), Somatic Symptom Scale (SSS-8), General Anxiety Disorder 7-item (GAD7), and Health Anxiety Inventory Short Form (HAI-S). The members of the Brain Fog Yes group also had to complete an adapted Cognitive Disturbance Scale. Finally, each participant underwent a comprehensive vestibular evaluation, including cervical and ocular vestibular evoked myogenic potential tests (c- and oVEMPs), video head impulse test (vHIT), and electronystagmography (ENG).

No significant difference was noted between the means of the two groups for age, sex, and racial composition. However, the mean total scores were higher for Brain Fog Yes group for PHQ-9, SSS-8, GAD-7, and HAI-S questionnaires. It was also established that the participants with higher total scores on these questionnaires were more likely to experience greater severity of brain fog. The severity was higher in males compared to females. PHQ-9, SSS-8, and GAD-7 were found to be good predictors of

brain fog severity while PQH-9, SSS-8, and HAI-S were good predictors of brain fog presence. Multiple logistic regression indicted that participants with vestibular migraine had odds of having brain fog 37% higher than those with other vestibular diagnoses. Overall, brain fog was defined as a cognitive condition, most frequently associated with such descriptors as “difficulty focusing”, “slow”, “difficulty thinking”, “forgetful”, and “exhausted.”

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KEY TO ABBREVIATIONS

aVOR: Angular vestibulo-ocular reflex

BPPV: Benign paroxysmal positional vertigo

BVD: Bilateral vestibular dysfunction

CFS: Chronic fatigue syndrome

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders

cVEMP: Cervical vestibular evoked myogenic potential

EMG: Electromyogenic

ENG: Electronystagmography

GAD-7: General Anxiety Disorder 7-item

HAI-S: Health Anxiety Inventory short form

HIT: Head impulse test

IVD: Initial vestibular diagnosis

LVST: Lateral vestibulospinal tract

MD: Meniere's disease

MLF: Medial longitudinal fasciculus

MVST: Medial vestibulospinal tract

NHIS: National Health Interview Survey

oVEMP: Ocular vestibular evoked myogenic potential

OKN: Optokinetic nystagmus

PHQ-9: Patient Health Questionnaire

POTS: Postural orthostatic tachycardia syndrome

SCC: Semicircular canals

SCDS: Superior canal dehiscence syndrome

SCM: Sternocleidomastoid

SSS-8: Somatic Symptom Scale

tVOR: Translation vestibulo-ocular reflex

UVD: Unilateral vestibular dysfunction

VCR: Vestibulocollic reflex

vHIT: Video head impulse test

VM: Vestibular migraine

VOR: Vestibulo-ocular reflex

VSR: Vestibulospinal reflex

CHAPTER 1: INTRODUCTION

The vestibular system in humans is composed of five neural structures on each side of the head: the utricle, the saccule, and the three semicircular canals. Three semicircular canals (SCC) (horizontal/lateral, anterior/superior, and posterior/inferior), arranged in orthogonal pairs, respond to angular acceleration near each canal's plane. The utricle and saccule comprise the otolith organs and respond to linear acceleration and deceleration, gravitational forces, and tilting of the head. The utricle senses tilt and linear horizontal head movements (side/side, front/back), and the saccule responds to vertical translations (up/down).

The sensations of linear acceleration and angular acceleration during head rotation are transferred from the vestibular end organs to the vestibular nuclei via secondary neurons, which play a crucial role in several vestibular reflexes, including the vestibulo-ocular reflex (VOR), the vestibulospinal reflex (VSR), and the vestibulocollic reflex (VCR). The neurons "sense" the changes in head position, and in response form synapses with the ocular motor nuclei that control the extra-ocular muscle movement patterns necessary for the VOR. The VOR plays a key role in gaze stabilization during high-frequency, high-velocity, and high-acceleration head movements. By measuring the VOR gain, phase, and symmetry, we can establish how well one's vestibular system works. Some of the clinical tests available to evaluate VOR function include ocular vestibular evoked myogenic potential (oVEMP) responses and the video head impulse test (vHIT). Cervical vestibular evoked myogenic potential (cVEMP) responses are employed to evaluate both the VCR and VSR.

Over the course of the last decade, a connection was established between vestibular dysfunction and cognitive impairment, including learning disability, deficits in executive functions, visuospatial abilities (e.g. spatial orientation, spatial memory, spatial navigation), attention, memory, as well as Alzheimer's disease and other dementias. A strong relationship between vestibular and psychiatric dysfunctions such as anxiety, depression, and panic disorder was also shown. In addition, some patients with vestibular dysfunction complain of brain fog.

Brain fog is a cognitive complaint, most frequently associated with forgetfulness, difficulty thinking, focusing, finding the right words, and feeling "cloudy." It is postulated that the symptom of brain fog is not related to a specific set of neuropsychological deficits that exist across these conditions, but rather to patients' subjective sense that these disease states subtly impair cognition in any number of ways. Clinically, it appears more common in patients with chronic rather than episodic vestibular symptoms, and most common in those with comorbid anxiety/depression or functional disorders like Postural Orthostatic Tachycardia Syndrome (POTS) and fibromyalgia. Despite multiple studies about brain fog, the full understanding of the condition, and even the precise definition of it are still missing. Thus, the main purpose of this study was to better understand the phenomenon of brain fog and its manifestation in patients.

In order to do so, we recruited 68 patients with an established diagnosis of vestibular pathology, from the Johns Hopkins Outpatient Neuro-Otology Center. The participants were separated into two groups (Brain Fog Yes and Brain Fog No) based on the presence of brain fogginess. Both groups partook in a four-part diagnostic

questionnaire, consisted of the Patient Health Questionnaire (PHQ-9), Somatic Symptom Scale (SSS-8), General Anxiety Disorder 7-item (GAD7), and Health Anxiety Inventory Short Form (HAI-S). Those from Brain Fog Yes group also completed an adapted Cognitive Disturbance scale. All participants also underwent a comprehensive vestibular evaluation consisted of Electronystagmography (ENG), VEMPs, and HIT tests. We believed that by understanding the exact meaning of brain fog and its expression in patients we would be able to determine if this phenomenon has an underlying psychiatric cause or has purely vestibular origins.

CHAPTER 2: LITERATURE REVIEW

Peripheral Vestibular System

The peripheral vestibular system is contained within the membranous labyrinth in the petrous portion of the temporal bone of each ear. The membranous labyrinth is filled with endolymph, an extracellular fluid rich in potassium and low in sodium and is suspended within the bony labyrinth by supportive connective tissue. The bony labyrinth is filled with perilymph, an extracellular fluid rich in sodium and low in potassium (Goldberg, 2015; Piker & Garrison, 2015). The vestibular apparatus is composed of five neural structures: the utricle, the saccule, and the three semicircular canals (Khan & Chang, 2013).

Three semicircular canals (SCC) (horizontal/lateral, anterior/superior, and posterior/inferior) respond to angular acceleration near each canal's plane. The canals are arranged as orthogonal pairs such that the anterior canals are roughly coplanar to the plane of the posterior canals of the opposite ear, whereas the horizontal semicircular canals lie in the same plane. Due to their orthogonal position to each other, the canals can sense the three-dimensional angular forces acting on the head (Piker & Garrison, 2015). However, since the SCCs are not precisely orthogonal with earth either horizontal or vertical, angular rotation of the head stimulates each canal to varying degrees (Schubert & Shepard, 2008). The lateral semicircular canals communicate with the utricle at both ends whereas anterior and posterior canals do so only at one end and join together at the other end (Piker & Garrison, 2015).

Each semicircular canal is dilated at the end closest to the utricle forming the ampulla which contains the sensory neuroepithelium called the crista ampullaris. The

crista contains sensory hair cells that are coated with a gelatinous substance, the cupula. The cupula acts as a barrier separating the endolymph of the SCC from the endolymph of the utricle (Piker & Garrison, 2015).

The mammalian vestibular system contains two types of hair cells: type I and type II. The type I hair cells are flask-shaped and are innervated by a calyx ending delivered from a single axon. One calyx nerve ending can synapse with up to four hair cells. The type II hair cells are cylindrically-shaped and have multiple afferent and efferent bouton nerve synapses (Goldberg, 2015). The apical end of each hair cell houses approximately seventy to a hundred stereocilia and a single tall kinocilium at one margin of the cell. The stereocilia are organized in rows with the tallest ones being the closest to the kinocilium and progressively decreasing in size to the shortest stereocilia (Khan & Chang, 2013).

Kinocilia and stereocilia respond to cupular deformation caused by the motion of endolymph which results in an opening or closing of the transduction channels of hair cells, which, in turn, changes the membrane potential of hair cells. Deflection of the stereocilia towards the kinocilia leads to excitation (depolarization), while deflection away from the kinocilia causes inhibition (hyperpolarization) (Schubert & Shepard, 2008). The kinocilia of the hair cells in the horizontal ducts are oriented toward the utricle, and the kinocilia of the anterior and posterior duct hair cells are oriented toward the duct. Thus, endolymph motion towards the ampulla causes depolarization in the horizontal SCC and hyperpolarization in the anterior and posterior SCCs (Khan & Chang, 2013). The cupula and endolymph have the same gravity preventing the cupula from the displacement by gravitational force. Angular head acceleration forces displace the cupula and bend the hair cells of the crista within each SCC. Stimulation of SCCs produces eyes

movement in the plane of that canal (Piker & Garrison, 2015). Endolymph flow that causes excitation in one semicircular duct will inhibit the hair cells of the contralateral duct it is paired with. Khan and Chang (2013) noted several advantages of such structural organization of the SCCs. Firstly, it allows the brain to establish the direction of head movement by comparing the signals received from the coplanar labyrinthine mates. Secondly, the central nervous system is programmed to ignore simultaneous firing of both semicircular ducts of the pair. Lastly, it allows to compensate for sensory overload.

The utricle and saccule construct the otolith organs. They respond to linear acceleration and deceleration, gravitational forces, and tilting of the head. The utricle senses tilt and linear horizontal head movements (side/side, front/back), and the saccule responds to vertical translations (up/down) (Piker & Garrison, 2015). Both the utricle and saccule house a sensory organ called the macula. Otoconia, small calcium carbonate particles, are contained in the otolithic membrane, within the macula (Khan & Chang, 2013). Vestibular receptor hair cells project through this otolithic membrane. Since the density of the otoconia is greater than that of the endolymph, the gravity force and linear acceleration can displace the otolithic membrane, bending the stereocilia. Depending on the cell polarity, the bending can either cause excitation, which is a result of an increase in the number of impulses in the vestibular nerve, or inhibition which is a result of a decrease in the number of impulses (Khan & Chang, 2013).

The stereocilia in the macula are oriented in relation to a central region known as the striola, which divides the otolith organs into two parts. Hair cells and their stereocilia are oriented in opposite directions on each side of the striola. In the utricle, the kinocilia and stereocilia of the hair cells are oriented toward the striola. In the saccule, they are

oriented away from the striola. While horizontal linear acceleration or static head tilt causes utricular excitation, vertical linear acceleration leads to saccular excitation (Schubert & Shepard, 2008). This pattern of response is critical to relating accurate information regarding the head position to the central nervous system.

The macula is also responsible for adaptation. For instance, when the head tilt stimulus remains beyond a few seconds, the bent hair cells and the depolarized membrane potentials begin to return to normal, allowing the hair cells to be responsive to further positional changes (Khan & Chang, 2013).

The hair cells of the crista ampullaris and the maculae send afferent impulses to the vestibular ganglion, also known as Scarpa's ganglia, which lie within the lateral portion of the internal auditory meatus, near the emergence of the vestibular nerve into the cerebellopontine angle (Schubert & Shepard, 2008). The vestibular ganglion consists of superior and inferior branches, which are connected by an isthmus. The cristae of anterior and horizontal canals, as well as the macula of the utricle, ascend their impulses to the superior division of the vestibular ganglion whereas the crista of the posterior SCC and the saccular macula communicate with the peripheral vestibular branches from the inferior section of the vestibular ganglion (Khan & Chang, 2013).

Central Vestibular System

Axons from the superior and inferior portions of the vestibular ganglion join the cochlear nerve to form the vestibulocochlear nerve, which enters the brainstem at the pontomedullary junction. At this point, the vestibular and cochlear nerves split from each other. While most of the afferent vestibular fibers project to the ipsilateral vestibular

nuclear complex in the pons, part of the nerve fibers project to the flocculo-nodular lobe of the cerebellum and the adjacent vermian cortex (Khan & Chang, 2013).

Vestibular Nuclear Complex

The vestibular nuclear complex contains four major nuclei: medial (Schwalbe), superior (Bechterew), lateral (Deiter), and inferior (descending). All four nuclei are positioned inferior to the floor of the fourth ventricle and project from the rostral medulla to the caudal pons in two major columns, the medial and lateral. The medial column is composed of the largest of the vestibular nuclei, the medial nucleus. The superior, lateral, and inferior vestibular nuclei construct the lateral column (Khan & Chang, 2013).

Axonal fibers from the cristae of the lateral SCCs ascend to the medial vestibular nucleus from where they travel to the motor nuclei of the extraocular muscles via the medial longitudinal fasciculus, to mediate the vestibulo-ocular reflex (VOR). The medial vestibular nucleus is also involved in the coordination of head and neck movement. It controls the vestibulospinal reflex (VSR) via bilateral descending projections in the medial vestibulospinal tract to the cervical spinal cord. The afferent input from the crista ampullaris of the superior and posterior SCCs project to the superior vestibular nucleus. Similar to the medial vestibular nucleus, it ascends efferent fibers to the extraocular muscles via the medial longitudinal fasciculus to coordinate the VOR (Khan & Chang, 2013).

The lateral vestibular nucleus receives afferent input from the crista ampulla, the maculae, and the vestibulocerebellum. Its efferent projections compose the lateral vestibular tract, which functions in the VSR by coordinating reflexive tone in the trunk muscles and proximal extensors of the limbs to maintain posture and balance. The

inferior vestibular nucleus receives afferent information from the maculae of both the utricle and the saccule, and its projections go to the other three vestibular nuclei and to the cerebellum (Lee et al., 2011).

Vestibulocerebellum

The cerebellum serves as an adaptive processor of the vestibular system. Its role is to monitor vestibular performance and to readjust vestibular input through inhibition as necessary. The floccolo-nodular lobe and the vermian cortex are the primary anatomical structures of the vestibulocerebellum. The ipsilateral cerebellum projects directly to the ipsilateral vestibular nuclei, and to the ipsilateral fastigial nucleus, which axons reach to the contralateral vestibular nuclei via the juxarestiform body. This area is crucial for the generation of postural reflexes and orienting behaviors. The cerebellar flocculus adjusts the gain of the VOR, while the cerebellar nodulus adjusts the duration of the VOR, as well as processes afferent activity from the maculae. The main role of the anterior superior vermis is the regulation of the VSR by encoding vestibular signals and proprioceptive input from the axial muscles. (Khan & Chang, 2013).

Vestibular Cortex

Multiple studies have established that the vestibular pathways project to the reticular formation, thalamus, cerebellum, through vestibular nuclei. These projections terminate into the cortical area, which, based on the functional magnetic resonance imaging, includes the parietal and insular regions (Dieterich & Brandt, 2015; Khan & Chang, 2013; Schubert& Shepard, 2016). Even though the vestibular cortex areas are found in both hemispheres, the inputs received from the stimulated ipsilateral vestibular end organs dominate over the contralateral stimuli. Since the brain cannot perceive two

different head motions or body postures simultaneously, one can infer the existence of a single “global vestibular percept,” where information from both sides of the head is combined via interhemispheric callosal communication (Dieterich & Brandt, 2015).

Despite the central vestibular system receiving sensory inputs from multiple areas along the vestibular pathway, the system does not have a primary sensory cortex, as the vestibular cortex neurons respond to stimulation from other senses (Dieterich & Brandt, 2015). The sensations of linear acceleration and angular acceleration during head rotation are transferred from the vestibular end organs to the vestibular nuclei via secondary neurons, which play a crucial role in several vestibular reflexes, including the VOR, the VSR, and the vestibulocollic reflex (VCR). By sensing the changes in head position, the neurons are able to form synapses with the ocular motor nuclei that control the extra-ocular muscle movement patterns necessary for the VOR (Piker & Garrison, 2015).

Vestibulo-Ocular Reflex (VOR)

Anatomy and Physiology of the VOR

According to Schubert and Shepard (2016), the primary purpose of the VOR is: To elicit rapid compensatory eye movements that maintain stability of images on the fovea (that part of the macula of the retina that is the most sensitive to clear visual viewing of objects in the visual field) during head motion. (p. 8)

The VOR is often thought of as a three-neuron arc projecting from the SCCs to the vestibular nuclei and then to the extraocular muscles to cause conjugate eye motion in a direction opposite to head turning (Khan & Chang, 2105; Schubert& Shepard, 2016). There are six extraocular muscles that control the position of the eye in the orbit: lateral rectus, medial rectus, superior rectus, inferior rectus, superior oblique, and inferior

oblique. The medial, superior, and inferior recti muscles, as well as the inferior oblique muscle, are innervated by the oculomotor nerve (cranial nerve III). The trochlear (cranial nerve IV) nerve innervates the superior oblique muscle, and the abducens (cranial nerve VI) nerve innervates the lateral rectus muscle (Eggers, 2016).

The position of the rectus muscles to the globe is posterior and medial to the axis of primary viewing. Oblique muscles approach the globe from anterior and medial positions relative to the axis of primary gaze. Contraction of the lateral and medial recti muscles produce a pure medial-lateral eye movement (yaw) when the axis of the primary gaze is directed upward, parallel to the plane of the horizontal canals. Contraction of other muscles produces complex eye movements in the yaw, pitch, and roll planes (Schubert& Shepard, 2016).

Carin and Santina (2004) stated that extraocular muscles are arranged in pairs that are roughly parallel to the respective SCCs that are the primary activators of the muscles on the ipsilateral side. Specifically, the medial and lateral recti muscles are aligned in a plane parallel to the horizontal canals. The superior and inferior recti muscles are aligned with the anterior SCC and the oblique muscles are parallel to the posterior canal. Simultaneous activation of the extraocular eye muscle pairs in proportions resembling the proportions of canal activation causes eye rotation in the direction opposite to the head movement (Carin & Santina, 2004; Schubert& Shepard, 2016). For instance, a head turn to the right causes the endolymph in the ampulla of the semicircular ducts to deflect the cupula to the left, causing depolarization of the hair cells on the right, and hyperpolarization of the hair cells on the left. Depolarized hair cells increase their firing rate in the afferent fibers of the right vestibular nerve, sending impulses to the ipsilateral

superior and medial vestibular nuclei as well as the cerebellum. Excitatory signals are transmitted in the medial longitudinal fasciculus to the right oculomotor nuclei, and in the ascending tract of Deiters to the left abducens nuclei. As a result, ipsilateral medial rectus and contralateral lateral rectus contract, producing eye movement to the left (opposite to head turning). Discrepancies of the eye and head velocity are regulated in the vestibular nuclei, where the mismatched input from the cerebellar floccolo-nodular lobe is sent to (Khan & Chang, 2013).

There are several subtypes of the VOR: the angular VOR (aVOR), canal-ocular reflexes receiving input from SCCs; the ocular vestibular evoked myogenic potential (tVOR), driven by otolith-ocular reflexes; otolith-mediated VOR, ocular counter-rolling, triggered by a change in the head's static orientation with respect to gravity in the roll (frontal) plane. Counter-rolling of the eyes (minimal change in the static torsion) occurs in the opposite direction with sustained head tilt (Schubert & Shepard, 2016).

VOR Gain and Phase

For the VOR to maintain a stable image on the fovea of the retina during rapid head movements, it requires the generation of compensatory eye movements in the direction opposite to the head movement. In the normally functioning system, the velocity of the eye movement is equal to that of the head movement. This relationship of the eye velocity to the head velocity is known as the gain of the VOR. Studies of Anson et al. (2016a) and Harun et al. (2016) claimed that a normal VOR should be equal to 1.0. The VOR gain less than 0.68 is considered as a cut-off point between normal and abnormally low VOR gain. Li et al. (2015) proposed that the VOR gain greater that 1.0 is considered disinhibition or "decalibration" of the VOR, indicating cerebellar

degeneration. Smith, Zheng, Horii, and Darlington (2005) stated that the VOR cannot recover normal response to high acceleration stimuli after damage to the vestibular system.

The timing relationship between the eye and head position is known as the VOR phase. Ideally, time arrival of the eye movement should coincide with the oppositely directed head position. Thus, eyes should be 180 degrees out-of-phase with head movement (Schubert & Shepard, 2016).

Shubert and Shepard (2016), with a reference to the study of Minor et al. (1999), stated that the VOR demonstrates velocity-dependent nonlinearities. Specifically, the VOR gain remains linear across frequencies of sinusoidal motions, with the peak velocity of 20 degrees/second. However, the gain becomes nonlinear for stimuli of higher frequencies and velocities. The researchers concluded that the VOR output may be a result of linear and nonlinear components combination (Schubert & Shepard, 2016).

Compensatory Eye Movements

The VOR plays a key role in gaze stabilization during high-frequency, high-velocity, and high-acceleration head movements (Carin & Santina, 2004). Similarly, the primary role of the ocular motor system is to stabilize gaze on the item of interest despite the item or head movement. If the image “slips” from the retina of the eye, visual acuity becomes degraded and the image is perceived as blurry. Several compensatory eye movements have evolved to provide high-resolution of a target image to the fovea, including saccades, smooth pursuit, optokinetic nystagmus, and vergence (Eggers, 2016; Piker & Garrison, 2015).

Saccades are rapid, brief, conjugate eye movements whose function is to place the image of interest onto the fovea. Saccades differ from other eye movements by the ability to move at a high velocity with the vision being impaired during the movement. There are several types of saccades: volitional, reflexive, predictive, memory guided, spontaneous, and to command (Eggers, 2016). Saccades interact with the vestibular system during the head movement in the following way: when the head turns, the VOR initiates a slow eye movement (the slow phase of nystagmus) in the direction opposite of head movement. After the vestibular system shifts the eyes from the original position, the saccadic system activates to bring the eyes back to the midline (fast phase of nystagmus). Nystagmus is a biphasic, repetitive, rhythmic involuntary movement with well-defined slow and fast phases (Piker & Garrison, 2015).

Smooth pursuit is the system employed to keep a slowly moving item of interest on the fovea of the retina when the head is stationary by matching target velocity with eye velocity. The system is primarily voluntary and gets activated when the target moves too slowly, so the system predicts where the target will be and accommodates for it. In the case of incorrect prediction or the target moving too fast, the saccadic system gets involved in redirecting the target image to the fovea (Piker & Garrison, 2015). The system is most effective for low-frequency and slow head movements (Carin & Santina, 2004).

The smooth pursuit system is also activated when the gaze is fixated on a stationary item during head movement. The VOR, triggered by the head movement, moves the eyes causing a slippage of the stationary target item from the fovea. This

causes the smooth pursuit system to override the VOR allowing one to fixate on the target. This phenomenon is known as fixation suppression (Piker & Garrison, 2015).

Optokinetic nystagmus (OKN) is a series of repetitive fast and slow eye movements generated by the optic flow of the visual scene. The main purpose of the OKN is to stabilize images on the retina during sustained head movements by moving the eyes in the same direction (Piker & Garrison, 2015). Optokinetic eye movements include a slow phase in the direction of the image motion and a nystagmus fast phase to reset the eye in the opposite direction (Eggers, 2016).

Vergence eye movement, as oppose to conjugate eye movement, moves the eyes in opposite directions so that the image of a single object is exposed to the fovea of each eye. Vergence is elicited by the loss of image sharpness (retinal blur) or retinal disparity that occurs when the distance to the target image changes (gaze shifts form a distant to a very close object; Eggers, 2016).

Vestibulocollic Reflex (VCR)

In contrast to the VOR, Goldberg and Cullen (2011) described the VCR as one of the less understood reflexes in mammals. According to the researchers, the function of the VCR is not completely clear, as the reflex can be thought of in two different ways. First, the VCR aims in head stabilization in space during active body movements, by generating a command to turn the head in the direction opposite to that of the current head-in-space motion. Second, the VCR possibly dampens head oscillation which could result from active head movements due to the head's mass. However, the authors noted that in mammals the VCR is weak, as head stabilization on the body is essentially absent for frequencies below the resonant frequency of the head.

The vestibulocollic pathway is believed to be trisynaptic, consisting of vestibulocollic neurons in the vestibular nuclei, motoneurons on the neck, and the peripheral synapse neurons. Both contralateral and ipsilateral inhibitory VCR pathways lead through the medial vestibulospinal tract (MVST) in the medial longitudinal fasciculus (MLF), as do ipsilateral inhibitory pathways, while ipsilateral excitatory pathways can run in the lateral vestibulospinal tract (LVST). The most direct pathways regulating some contralateral inhibition in vertical canal-related pathways include a commissural inhibitory neuron located in the cervical spinal cord (Goldberg & Cullen, 2011). Ashford and colleagues (2016), on the other hand, stated that the synaptic organization of the VCR in human is not fully understood and requires further research. It is known that the VCR controls a complex musculature. Every particular head movement activates a particular muscle pattern (Goldberg & Cullen, 2011).

While the VCR relates to head movement, Janky and Shepard (2016) stated that the primary goal of the VSR is body stabilization for postural control. The VSR is composed of three primary tracts, including lateral vestibulospinal, medial vestibulospinal, and reticulospinal. The VSR is a complex system as it involves multiple muscles connection throughout the body such as the neck, arms, hands, legs, feet, etc.

Tests of Vestibular Function

A battery of tests is necessary to assess the vestibular physiological reflexes at the peripheral and central levels of the system. Some of the clinical tests available to evaluate VOR function include ocular vestibular evoked myogenic potential (oVEMP) responses and the video head impulse test (vHIT). Cervical vestibular evoked myogenic potential (cVEMP) responses are employed to evaluate both the VCR and VSR (Zalewski, 2015).

Cervical Vestibular Evoked Myogenic Potentials (cVEMPs)

The cervical vestibular evoked myogenic potential (cVEMP) test is an accepted clinical tool for testing the saccular function and the inferior vestibular nerve integrity (Maheu, Houde, Landry, & Champoux, 2015). The saccular afferents are activated by intense tone burst, click, and bone-vibratory stimuli. The activation leads to inhibition of the sternocleidomastoid (SCM) muscle via the vestibulocollic pathway (Ashford et al., 2016). The inhibitory potentials can be measured with surface electrodes placed over the SCM muscle and are characterized by two distinct peaks: a positivity known as the p13 and a negativity known as the n23. The evoked responses are primarily ipsilateral in nature. Cervical VEMPs are considered to be a relaxation response in a tonically contracting muscle. Being a reliable test of saccular function, cVEMPs are widely used in the clinical diagnoses of superior canal dehiscence syndrome (SCDS), acoustic neuromas, Meniere's disease, vestibular neuritis, multiple sclerosis, and lower brainstem lesions (Nguyen, Welgampola, & Carey, 2010). According to the study of Nguyen et al. (2010), cVEMPs evoked by a reflex hammer tapping have excellent reliability, while the responses evoked with Mini-Shaker and auditory stimuli have fair-to-good reliability.

Ocular Vestibular Evoked Myogenic Potentials (oVEMPs)

The ocular VEMPs can be evoked by the same stimuli types as the cVEMPs. The vibration-evoked oVEMPs are believed to evaluate the utricular and superior vestibular nerve function (Agrawal et al., 2012; Maheu et al., 2015). The responses can be recorded on upgaze with surface electrodes placed inferior to the eyes (1 cm and 3 cm below the center of each lower eye lid) and represent the contralateral pathway, where stimulation of one ear affects the extra-ocular muscles on the opposite side. Ocular VEMP responses

have a negative peak at 10 ms, called the n10 potential, and the positive peak occurring at 16 ms referred to as the p16 potential (Nguyen et al., 2010). Vibration-evoked oVEMPs are found to be useful in the diagnosis of superior vestibular neuritis, vestibular schwannoma, and SCDS, showing abnormal or reduced waves morphology. The researchers also showed that the oVEMP responses yielded excellent reliability in response to vibrational and sound stimuli (Nguyen et al., 2010).

Head Impulse Test (HIT)

The head impulse test (HIT) is a test used to specifically evaluate the VOR function in each of the 6 semicircular canals. The vestibular function is measured by a head turn in the direction of both horizontal and vertical planes. The SCC dysfunction in the direction of head rotation leads to corrective saccade in a latency range of 70-200ms to maintain gaze fixation (Agrawal et al., 2013). According to Anson et al. (2016a), employment of video HIT (vHIT) technology allows to detect and quantify compensatory saccades, permitting quantitative assessment of rotational vestibular function. Researchers described compensatory saccades as an oculo-motor gaze-stabilizing strategy aiming to compensate for a deficient VOR. The presence of saccades, as well as their morphology (latency and intensity), provides information about underlying VOR function. Healthy older individuals, however, show significantly larger compensatory saccades, even when the low VOR is compensated for. Anson et al. (2016b) explained this phenomenon by the fact that even slight reduction of the VOR gain with age may trigger compensatory saccades. The researchers proposed that the amplitude of the compensatory saccades may serve as a sign of the gaze stabilization ability decline in older subjects, along with VOR gain.

Effect of Normative Aging on Vestibular Test Outcome

Nguyen et al. (2010) showed a significant decrease in amplitudes of cVEMP and oVEMP responses in adults older 50 years of age in response to click, toneburst, and a reflex hammer tap stimuli. However, their study found no significant association between age and amplitudes, latencies, and asymmetry ratios of either responses, when age was treated as a continuous variable. Even though Janky and Shepard (2009) noted on a general agreement in the literature that cVEMP amplitudes decrease with age, their study failed to demonstrate the effect of age on cVEMP amplitudes for 250, 500, 750, and 1000 Hz tone stimuli. They did, however, find a significant positive correlation between age and cVEMP thresholds for tonebursts, at all test frequencies. No inter-group age differences in thresholds were noted for click stimuli. Agrawal and colleagues (2012), on the contrary, concluded that cVEMP amplitudes show a significant decrease with aging, suggesting a decreased saccular function in older individuals.

Maheu et al. (2015) reported that the effect of normal aging on oVEMPs is expressed in decreased response amplitudes and increased thresholds, significant for adults after 60 years old. Piker, Jacobson, McCaslin, and Hood (2011) found only 77% of their study participants age 50 years and older showed present oVEMP responses, while a response rate of 100% was observed for subjects younger than 50 years of age. Additionally, researchers noticed an increase in thresholds and decrease in amplitudes for the group of adults 50 years of age and older. Similar to the findings from the study of Nguyen et al. (2010), no age effect was noted on oVEMP latencies. Agrawal et al. (2012) reported significantly decreased n1 amplitude for individuals 70 years of age and older.

Agrawal et al. (2013) observed that abnormal horizontal vHIT was associated with low gait speed and higher fall risk in individuals 70 years of age and older. Similarly, Maheu and colleagues (2015) claimed that the literature reports a minor effect of age on the vHIT gain. Specifically, only posterior SCCs were found to show a slight decrease in gain with age increase. According to the researchers, significant gain differences were noted only for individuals of 90 years of age and older. The authors stated that vHIT should be given a preference over caloric testing when evaluating function of the vestibular SCCs, given vHIT's noted independence of normal aging.

Vestibular System in Healthy Older Adults

Several studies remarked that neuroanatomic age-related changes of the peripheral and central vestibular systems can be accountable for the observed decreased vestibular function in older adults (Agrawal et al., 2012, 2013; Janky & Shepard, 2009; Maheu et al., 2015; Piker et al., 2011; Zalewski, 2015).

Agrawal et al. (2012) aimed to evaluate how the normative aging affects vestibular end organ function in adults age 70 years and older. One of the primary goals of the research was to examine if aging causes dysfunction predominantly in the semicircular canals or the otolith organs. A global decline in function associated with aging was noted in all five vestibular end organs. However, the data suggested that the degree of the decline was asymmetrical across the vestibular apparatus: while bilateral SCC dysfunction was noted in 82-94% of the adults age 70 and older, only 54-62% of participants demonstrated dysfunction in saccular performance. Finally, the utricular performance was affected the least, with 18-24% of the study participants showing impairment in that organ (Agrawal et al., 2012).

Johnsson (1971) discovered that elderly people with saccular maculae degeneration had loss of otoconia. While the utricular macula undergoes some degree of degeneration as well, it is not as significant, compared to the saccule. Rosenhall (1973) showed a reduction of the hair cells condensation up to 20% in the otolithic maculae in adults 70 years or age or older. The hair cell loss in the semicircular canals cristae can reach up to 40%. Zalewski (2015) stated that there is a universal agreement in the literature that vestibular cells degenerate at almost every level of the vestibular pathway, including the SCC and the otolith organs, the nerve fibers, Scarpa ganglion cells, vestibular nuclei neurons, and a certain cell type within the cerebellum in adults 60 years of age and older.

An association between vestibular dysfunction and fall risk has been established in multiple studies (Agrawal et al., 2012; Agrawal et al., 2013; Maheu et al., 2015; Zalewski, 2015). Bilateral vestibular loss was found to cause more incidents of falls compared to unilateral loss or normally functioning systems (Agrawal, Davalos-Bichara, Zuniga, & Carey, 2013). Anson et al. (2016a) showed a significantly higher occurrence of saccades made by healthy older adults compared to younger individuals. The researchers also noted that, besides causing a decrease in VOR gain, aging of the vestibular system can affect gaze stabilization by other mechanisms.

Vestibular Dysfunction and Cognitive Impairment

Over the course of the last decade, multiple studies claimed that there is an association between vestibular dysfunction and cognitive impairment, including learning disability, deficits in executive functions, visuospatial abilities (e.g. spatial orientation, spatial memory, spatial navigation), attention, memory, as well as Alzheimer's disease

and other dementias (Bigelow & Agrawal, 2015; Bigelow et al., 2015; Harun et al., 2016; Previc, 2013; Smith et al., 2005). The study of Bigelow, Semenov, du Lac, Hoffman, and Agrawal (2016) showed a strong relationship between vestibular and psychiatric dysfunctions such as anxiety, depression, and panic disorder. The study also showed that combined, vertigo-related anxiety, depression, and panic attacks accounted for 32% of the effect of vestibular vertigo on difficulty remembering, indicating that substantial portion of the cognitive impairment seen in vertigo patients is caused by the underlying psychiatric disorder (Bigelow et al., 2016).

Odman and Maire (2008) stated that vestibular dysfunction can cause somatopsychic anxiety and anxiety, on its turn, can lead to psychosomatic dizziness. According to Staab (2016), patients suffering from panic attacks with dizziness reported as the primary symptom, were found to be more likely to complain about experiencing light-headedness, nonspecific swirling sensation, and head fogginess. The researcher also claimed, with the reference to the previous research, that patients with anxiety disorders are likely to demonstrate nonspecific, non-diagnostic abnormalities (slightly higher gain and shorter latencies of the canal – and otolith-ocular reflexes) on the tests of semicircular canal function, with unclear etiology of the above abnormalities (Staab, 2016).

Based on the cross-sectional study that used the 2008 National Health Interview Survey (NHIS) that incorporated questions about balance and dizziness, Bigelow and colleagues (2016) showed that people suffering from vestibular dysfunction are three times more likely to develop anxiety, panic disorder, or depression. While investigation psychiatric comorbidity in different organic vertigo syndromes, Eckhart-Henn and

colleagues (2008) discovered that as many as 65% of patients diagnosed with vestibular migraine (VM) and 57% with Meniere's disease (MD) had comorbid anxiety, phobic disorders, and/or depression. Gurvich et al. (2013), on the other hand, claimed that the best predictor of depression and anxiety in patients with vestibular disorders was the patients' level of distress associated with symptoms of dizziness or vertigo, rather than the particular disorder itself.

As the outcome of their study, Bigelow et al. (2016) concluded that due to the high comorbidity of vestibular dysfunction and affective disorders, the mental distress in these patients can cause functional impact and necessitate treatment. Thus, patients with symptoms of vestibular vertigo should be screened for comorbid psychiatric condition and referred to mental healthcare providers when necessary.

Despite the attempts of multiple studies to investigate the relationship between vestibular loss and cognitive impairment, the exact mechanism by which the two are associated is still unclear (Bigelow & Agrawal, 2015; Bigelow et al., 2015; Bigelow et al., 2016; Harun et al., 2016; Previc, 2013; Semenov, Bigelow, Xue, du Lac, & Agrawal, 2016). It is known, though, that both vestibular and cognitive function share common risk factors, such as microvascular disease and hyperglycemia (Bigelow et al., 2015). According to the researchers, there are several hypotheses explaining potential pathways discussed in the literature. Bigelow and colleagues (2015) and Semenov et al. (2016) discussed three possible associations between vestibular and cognitive functions. Firstly, deficit or loss of peripheral vestibular input can cause atrophy of areas within the dorsal thalamus, the temporo-parietal junction, and the hippocampus, which, in its turn, may result in visuospatial memory and perception dysfunction. Secondly, the possible

association between vestibular and cognitive impairment may relate to decrease in cognitive resources when a vestibular loss occurs. Vestibular loss leads to increased instability in gaze and posture which may require allocation of additional attention resources for maintenance of balance and orientation, decreasing cognitive reserve available for other tasks, especially the ones processed by similar cognitive networks. Thus, it seems like the brain prioritizes falls prevention over other cognitive tasks (Bigelow & Agrawal, 2015). Finally, there is a known association between vestibular loss and affective disorders, such as depression and anxiety, which may, in turn, lead to cognitive dysfunction (Semenov et al., 2016).

As reported in Bigelow and Agrawal (2015), the vestibular system activates cortical areas such as the insula, superior temporal gyrus, hippocampus, and the inferior parietal lobule. These cortical areas are also involved in the complex neural network for visuospatial processing and memory. The hippocampus and the basal ganglia are thought to house spatial working memory centers which serve as the short-term storage of spatial information used in the ongoing cognitive tasks, with vestibular input playing a crucial role (Bigelow et al., 2015).

Neuro-imaging of patients with bilateral vestibular dysfunction (BVD) revealed selective atrophy of the hippocampal area of the brain (Harun et al., 2016; Smith et al., 2005). Patients with BVD showed a decrease of the hippocampal area up to 16.9 % with impaired spatial memory, while patients affected by unilateral vestibular dysfunction (UVD) demonstrated no changes in hippocampal volume or spatial memory. Instead, they showed a reduction in temporal gyrus volume (Bigelow & Agrawal, 2015). Previc

(2013) stated that the greater effect of the BVD on the hippocampal region relative to UVD may explain the preference of unilateral labyrinthectomy to treat Meniere's disease

In their literature overview study, Bigelow and Agrawal (2015) reported links between vestibular and cognitive function. According to the researchers, BVD was associated with impaired visuospatial ability while UVD leads to no greater than mild changes in performance on tests assessing spatial memory. Patients with UVD were, however, found to have comorbid depression and anxiety. Vestibular dysfunction was also found to negatively affect the navigational ability of a person, especially when visual cues are not available. Luckily, compensatory navigational strategies can be developed, allowing for improvement of spatial navigation abilities by means of vestibular therapy. Smith et al. (2005), on the other hand, stated that despite compensatory mechanisms activated following vestibular damage, many of the ocular motor and postural symptoms either do not compensate or compensate incompletely. Specifically, the VOR, according to the researcher, never recovers its normal response to high acceleration stimuli.

Brain Fog

Some patients diagnosed with vestibular disorders complain of experiencing brain fog. Several studies have investigated the brain fog phenomenon (Ross, Medow, Rowe, & Stewart, 2013; Wise, Ross, Brown, Evans, & Jason, 2017). Ross and colleagues (2013) attempted to define the meaning of the term "brain fog", as well as its etiology and possible treatment options. The researchers found that patients suffering from postural tachycardia syndrome (POTS), a chronic form of orthostatic intolerance, listed brain fog among the top cognitive impairment complaints. Brain fog is a cognitive complaint, most frequently associated with forgetfulness, difficulty thinking, focusing, finding the right

words, and feeling “cloudy.” The least frequently words used to describe the phenomenon were “thoughts moving too quickly,” “detached,” “lost,” “sleepy,” and “annoying” (Ross et al., 2013).

Wise et al. (2017), established that individuals with severe fatigue had significantly higher frequency of episodes, longer duration and greater average number of hours of brain fog per day. Also, these individuals had more frequent fatigue caused by orthostatic intolerance, and more hours a day spent laying down. Individuals with more severe expression of brain fog symptomology were found to be significantly more likely to report being “confused”, “forgetful”, “exhausted”, “sleepy”, “lost”, and their “thoughts moving too fast” as the description of having a brain fog.

Ocon (2013) discussed brain fog in association with a mild cognitive impairment in patients with chronic fatigue syndrome (CFS). The author continued that patients affected by brain fog often experience deficits in working memory, processing information, and attention causing extended reaction time. Finally, he concluded that while cognitive impairment in CFS patients can be exacerbated by stress and impaired cardiovascular system, psychiatric diseases do not seem to be related to brain fog (Ocon, 2013).

According to Dr. Staab, an expert in the practice of psychosomatic medicine from the Mayo clinic, the list of conditions that cause foggy thinking is robust: “chemo brain” in cancer, “pump brain” in cardiac surgery, “fibro fog” in fibromyalgia, “brain fog” in many others. It is postulated that the symptom of “brain fog” is not related to a specific set of neuropsychological deficits that exist across these conditions, but rather to patients’ subjective sense that these disease states subtly impair cognition in any number of ways.

Clinically, it appears more common in patients with chronic rather than episodic vestibular symptoms, and most common in those with comorbid anxiety/depression or functional disorders like POTS and fibromyalgia (Y. Agrawal, personal communication, October 12, 2017). According to Ross and colleagues (2013), brain fog can be triggered by physical fatigue, dehydration, lack of sleep, extended standing, and feeling faint.

Lastly, Wise and colleagues (2017) established that physical counter activities, such as walking, physical therapy, or even caffeine consumption, help to improve brain fog symptoms for individuals with a milder form of the symptomology compared to the ones with the severe form of brain fog. Interestingly, Ross et al. (2013) stated that for patients with POTs, lying down, high intake of fruit, heat avoidance, and consumption of at least 16oz of water in less than 5 minutes period, and high salt diet, helped to alleviate brain fog symptoms. On the contrary, showering, physical exercises, walking, and caffeine reportedly made brain fog worse.

Despite multiple studies about brain fog, the full understanding of the phenomena, and even the precise definition of it are still missing. The goals of the current study are:

1. Understand what exactly is brain fog and how it manifests in patients.
2. Identify psychiatric confounders and characterize the previously unexamined phenomena of vestibular brain fog.
3. Ascertain if the issue at hand is due to an underlying psychiatric condition or is vestibular in nature, by examining patient records and by conducting patient interviews.

In summation, we hypothesize that an underlying vestibular condition is resulting in a psychiatric disorder that then manifests in the patient experiencing brain fog.

CHAPTER 3: METHODS AND MATERIALS

Methods

Subject Recruitment

The study included 68 participants of both genders, ages 22 through 85 years old. The subjects were recruited through the Johns Hopkins Outpatient Neuro-Otology Center. The primary inclusion criterion was the presence of any vestibular diagnosis at the time of the study. Written consent was obtained from all participants.

To comply with the recommendations of Bigelow et al. (2016), all participants were screened for psychiatric conditions, often comorbid with the vestibular abnormalities. The subjects were separated into two groups (Brain Fog Yes and Brain Fog No) based on the presence of brain fogginess. Both groups partook in a four-part diagnostic questionnaire, consisted of the Patient Health Questionnaire (PHQ-9), Somatic Symptom Scale (SSS-8), General Anxiety Disorder 7-item (GAD7), and Health Anxiety Inventory Short Form (HAI-S). Participants from the Brain Fog Yes group also had to complete adapted Cognitive Disturbance Scale. All participants also underwent comprehensive vestibular evaluation consisting of Electronystagmography (ENG), VEMPs, and HIT tests.

Questionnaires

PHQ-9

The Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001) is a standardized nine-question self-administered depression module. It covers each of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for depression and scores each question on the scale from “0” (not at all) to “3” (nearly every day).

Based on the outcomes of their study, researchers showed that scores greater than or equal to 10 had a sensitivity of 88% and a specificity of 88% for major depression (Kroenke et al., 2001). Given these criteria, a binary depression variable was created, with scores greater than or equal to10 on the PHQ-9 total score stratified as having depression, and those below 10 classified as having no depression. In addition, the PHQ-9 also classifies depression, by designating scores of (0-5), (5-10), (10-15), (15- 20), (20-27) to represent no, mild, moderate, moderately severe, and severe depression (Kroenke et al., 2001). From that information, a categorical variable was created to compare the 5 classifications of depression. A continuous variable to compare the total PHQ-9 score was also created.

SSS-8

The Somatic Symptom Scale (SSS-8; Gierk et al., 2014) is a self-reported outcome measure of somatic symptom burden. This eight-item screening tool were scored on a "0" (not at all) to "4" (very much) scale. The SSS-8 severity categories was calculated in accordance with percentile ranks: no to minimal (0-3 points), low (4-7 points), medium (8-11 points), high (12-15 points), and very high (16-32 points) somatic symptom burden (Gierk et al., 2014). In order to analyze the data, we created an SSS-8 total continuous variable and an SSS-8 categorical variable that consisted of the 5 categories of the SSS-8 burden.

GAD-7

The General Anxiety Disorder (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006) scale was utilized to screen for General Anxiety Disorder (GAD) for each participant. The seven-question screening tool was scored on a scale from "0" (not at all

sure) to “3” (nearly every day). The test has a sensitivity of 89 % and a specificity of 82% to identify GAD (Spitzer et al., 2006). For statistical analysis, the GAD-7 data was organized three ways. First, the data was categorized by the score clusters of 0-5, 5-10, 10-15, 15-21 corresponding to no, mild, moderate and severe anxiety, respectfully. Second, a cut off score of 10 or greater was set to identify probable GAD, as a binary variable (Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007). Third, we utilized the total GAD-7 score to compare as a continuous variable.

HAI-S

The Health Anxiety Inventory Short Form (HAI-S; Salkovskis, Rimes, Warwick, & Clark, 2002) was utilized to screen and quantify hypochondriasis for each participant. The fourteen-question screening tool was scored on a scale from 0 to 3, with a higher value indicating the higher severity of the symptoms (Salkovskis et al., 2002). A continuous variable to compare HAI-S total scores was then created.

Cognitive Disturbance Scale

The Cognitive Disturbance Scale is a multipart scale adapted from Ross et al. (2013). Only patients that identify themselves as feeling “foggy” had to answer this questionnaire. The questionnaire involves a 21-symptom scale where each symptom severity is scored 0-100. The questionnaire also inquires to the frequency of the brain fog where 0 is “very infrequent” and 4 is “very frequent”. In addition to frequency, the questionnaire also probes into the time of day that the symptom occurs. A variable was created for each symptom, severity, time and frequency. In addition, a variable was created to sum up all the patient’s individual brain fog severity scores and divided by 21 to create a continuous Brain Fog Score Mean. The frequency was factored in by changing

the scale of 0-4, to 0, 25, 50, 75, 100. The scores were then totaled for each participant and divided by 21 to create a mean Frequency score. To create a total brain fog score variable, the mean scores of the severity and the frequency were combined and divided by two to keep the score under 100.

Vestibular Assessment

Electronystagmography

A standard ENG test battery, including oculomotor, positional, and caloric tests were employed to identify the presence of gaze, saccade, pursuit, or optokinetic eye movements. All tests were administered in a dark room, with participants either sitting or lying down. Prior to the testing, each participant's face was cleaned with an alcohol-saturated cotton pad and allowed to air-dry. Five electrodes were applied using adhesive tape and paste. One electrode was positioned in the center of a forehead, two electrodes were positioned above the eyebrow and below the eye in a way that allows a participant to close eyes, and two electrodes were positioned to the side of each eye. Electrodes impedance testing was done to ensure proper connection.

Patients were sitting for ocular motility testing and lying down for positional testing. Bio-calibration was done by asking the patent to look at the lights on calibration bar alternately from right to left which was placed at the foot end of the patient. After the machine was calibrated, recording of ENG was done first for spontaneous nystagmus with eyes closed followed by gaze nystagmus to 30 degrees right and left, pendular eye tracking test, optokinetic test and positional test in five head positions (supine, head right and left, body right and left). Dix-Hallpike maneuver was performed to provoke benign paroxysmal positional vertigo (BPPV).

For a caloric portion of the test, patients were lying down supine on a gurney with eyes closed and head end raised by 30 degrees above the horizontal, to bring the horizontal semicircular canal in the vertical plane where they could be maximally stimulated. Caloric testing is a quantitative "go to" procedure for identification of presence and side of peripheral vestibular hypofunction (Park, Migliaccio, Santina, Minor, & Carey, 2005). The test was performed using a temperature-switch irrigation technique at 30.5 and 43.5 degrees Celsius for cold and hot water conditions, respectfully. Horizontal eye movements were recorded using electrooculography with the eyes closed. The maximum velocity of the slow-phase component of nystagmus was analyzed for unilateral weakness (UW). Analysis of the data was restricted to the initial 150 ms after onset of the stimulus, indicating the minimal effect of the non-vestibular systems (the smooth pursuit, optokinetic, and predictive oculomotor systems). The latter generally have longer latencies relative to VOR.

Vestibular Evoked Myogenic Potential Recording Conditions

Ocular and cervical vestibular evoked myogenic potential testing was performed. The test parameters were based on the study of Li, Layman, Carey, and Agrawal (2015b). A commercial electromyogenic (EMG) system (Carefusion Synergy, software version 14.1, Dublin, OH, USA) was used. EMG signals was recorded with disposable, self-adhesive, pregelled, Ag/AgCl electrodes with 40-inch safety lead wires from GN Otometrics (Schaumburg, IL, USA). EMG signals were amplified 2500x and band-pass filtered, 20-2000 Hz for cVEMPs, 3-500 Hz for oVEMPs (Li et al., 2015b).

Ocular VEMPs

Participants laid with upper bodies elevated at 30 from horizontal. The skin overlying both cheeks and the manubrium sterni was cleansed with alcohol preps before electrode placement. A noninverting electrode was placed on the cheek approximately 3 mm below the eye, directly beneath the pupil, an inverting electrode was placed 2 cm below the noninverting electrode and a ground electrode was placed on the manubrium sterni. Before stimulation, participants were instructed to perform 20-degree vertical saccades to ensure that symmetrical signals are recorded from both eyes. In the experimental set-up, the participant's eye level was marked on the wall next to the participant's chair and targets on the ceiling was measured and marked to elicit the 20-degree vertical saccades with the participant's eyes at the specified level. If signals showed greater than 25% asymmetry, the electrodes were removed, and new ones were applied. Participants were instructed to maintain a 20 upgaze during oVEMP stimulation and recording. Midline vibration stimuli consisted of head taps was delivered manually with an Aesculap model ACO12C reflex hammer fitted with an inertial microswitch trigger. Head taps were delivered at Fz, in the midline at the hairline, 30% of the distance between the inion and nasion. Fifty sweeps for head taps were averaged for each test.

Cervical VEMPs

Participants laid with upper bodies elevated at 30 from horizontal. The skin overlying both sternocleidomastoid (SCM) muscles and the manubrium sterni was cleansed with alcohol preps before electrode placement. A noninverting electrode was placed at the midpoint of the SCM muscle, an inverting electrode was placed on the sternoclavicular junction, and a ground electrode was placed on the manubrium sterni.

Participants were instructed to lift their heads up from the head rest to provide tonic background SCM activity during stimulation and recording, and a pre-stimulus rectifying surface EMG signal of at least 30 μV over 10 ms was required for accepting a cVEMP tracing. Air-conducted sound stimuli consisted of 500 Hz, 125 dB SPL tone bursts of positive polarity, with a linear envelope (1 ms rise/- fall time, 2 ms plateau), at a repetition rate of 5 Hz. Sound stimuli were delivered monaurally through Audiocups, noise-excluding headset enclosures from Amplivox (Eden Prairie, MN, USA).

VEMPs Response Parameters

The oVEMP waveform consists of a negative peak (n10), identified as the first distinctive peak in the waveform, followed by a positive peak (p16), identified as the first distinctive trough in the waveform. Subjects with EMG recordings lacking definable n10 waves were defined as having an absent VEMP response. Latencies of the n10 peak were averaged between the two sides for subjects with bilateral oVEMP responses. The peak-to-peak amplitude was calculated as the sum of the n10 and p16 amplitudes. Asymmetry ratio (AR) between a subject's ears was calculated according to the formula: AR = (Left amplitude - Right amplitude / Left amplitude + Right amplitude) x 100%.

The cVEMP waveform consists of a positive peak (p13), identified as the first distinctive trough in the waveform, followed by a negative peak (n23), identified as the first distinctive peak in the waveform. Background EMG activity was recorded during the 10-ms interval before stimulus onset. Subjects with EMG recordings lacking definable p13 waves were defined as having an absent VEMP response. Latencies of the p13 peak were averaged between the two sides for subjects with bilateral cVEMP responses. The raw peak-to-peak amplitude was calculated as the sum of the p13 and n23 amplitudes and

rectified amplitude was calculated by the raw peak-to-peak amplitude by the background activity. Asymmetry ratio (AR) was calculated using the above formula.

Video Head-Impulse Test

The video head-impulse test was administered following the parameters described in Li et al. (2015a). The ICS Impulse 3-D vHIT system (GN Otometrics, Schaumburg, IL, USA) was used. The vHIT system consists of a high-speed digital video camera, a mirror to reflect the eye to the camera, and an inertial measurement unit, all mounted to a lightweight glasses frame. Because individuals have been shown to adapt their VOR gain according to the rotational magnification induced by habitual use of corrective spectacles (i.e., glasses), subjects were instructed to remove corrective spectacles for a minimum duration of 5 minutes before testing. The right eye was illuminated by two infrared light-emitting diodes and eye position was calibrated with projected targets from a glasses-mounted laser. Subjects were instructed to fixate on a stationary target projected 124 cm ahead at eye level. Approximately 10 horizontal head impulses to each side were manually applied with unpredictable direction and timing. Peak head velocity ranged typically from 150 to 200 degrees per second. The right eye position was recorded at 250 Hz and velocity was acquired from a two-point differentiator and low-pass filtered (0-30 Hz bandwidth). Recordings in which the eye movement appeared to precede the head movement have been shown to represent goggle slippage. If this pattern was observed during vHIT testing, attempts were made to improve goggle fit, including tightening the goggle frame and trying to vary the position of the goggles on the orbital rim.

CHAPTER 4: RESULTS

The aim of this study was to better understand brain fog and its manifestations in patients by examining the underlying conditions of the phenomenon. The results section will be organized in the following way. First, the overall characteristics of the study sample will be discussed in terms of its demographics, initial vestibular diagnoses, and presence of brain fogginess. Next, the outcomes of the Cognitive Disturbance Scale questionnaire will be discussed to evaluate the descriptive characteristics of the individuals with brain fog. Lastly, the outcomes of the logistic and linear regression analyses will be presented to establish the predictors of the brain fog.

Sample Characteristics

Demographic composition of the study participants is given in Table 1. Sixty-eight participants were recruited, of whom 21 were males (30.9%) and 46 (67.6%) females. The mean age of the participants was 56.49 years (*SD* = 14.14). Fifty-three participants (77.9%) were white, 10 (14.7%) were black, and 4 (5.9%) were classified as others. Age, sex, and gender of 1 participant are unknown. From the overall sample, 39 participants had brain fog (11 males [28.2%], 28 females [71.8%]) and 29 did not (10 males [34.5%], 18 females [62.1%]). In the Brain Fog Yes group, 32 (82.1%) participants were white, 5 (12.8%) black, and 2 (5.1%) identified as other race. Among participants of the Brain Fog No group, 21 (72.4%) were white, 5 (17. 9%) were black, and 2 (6.9%) identified as other race. The participant with unknown age, sex, and gender belonged to the Brain Fog No group. Independent 2-tail t-tests did not reveal significant difference for age ($t(65) = -1.766$, $p = .082$), sex ($t(65) = 0.646$, $p = .521$), and race ($t(65) = -0.643$, $p = .522$) between the Brain Fog Yes and Brain Fog No groups.

Table 1

Overall Demographic Characteristics of the Sample by Brain Fog

	Sample		
	Overall (N = 68*)	Brain Fog Yes (N = 39)	Brain Fog No (N = 29)
Characteristics	*Mean (SD) n(%)*	*Mean (SD) n(%)*	*Mean (SD) n(%)*
Age	56.49 (14.14)	53.95 (12.44)	60.04 (15.76)
Sex			
Male	21 (30.9)	11 (28.2)	10 (34.5)
Female	46 (67.6)	28 (71.8)	18 (62.1)
Race			
White	53 (77.9)	32 (82.1)	21 (72.4)
Black	10 (14.7)	5 (12.8)	5 (17.9)
Other	4 (5.9)	2 (5.1)	2 (6.9)

Note. * = sex, age, and gender of 1 participant are unknown.

Pearson product-moment correlation was calculated to determine the relationship between brain fog and initial vestibular diagnosis. There was a strong, negative statistically significant correlation between brain fog and initial diagnosis ($r(63) = -.310$, $p = 0.013$), indicating that participants with vestibular migraine would be more likely to have brain fog compared to those with bilateral vestibular loss. Figure 1 displays a visual representation of the vestibular diagnoses found in the study by brain fog. In the Brain Fog Yes group, vestibular migraine ($n = 21$) was the most common diagnosis, followed by Meniere's disease ($n = 7$), bilateral vestibular loss ($n = 4$), benign paroxysmal positional vertigo ($n = 2$), cerebellar ataxia ($n = 1$) and vertebrobasilar insufficiency ($n = 1$). Vestibular migraine was also prevalent in Brain Fog No group ($n = 8$), followed by BPPV ($n = 6$), unilateral vestibular loss ($n = 6$), Meniere's disease ($n = 3$), bilateral vestibular loss ($n = 3$), cerebellar ataxia ($n = 1$), and superior canal dehiscence ($n = 1$). Initial diagnosis of 4 participants (3 Brain Fog Yes, 1 Brain Fog No) is unknown.

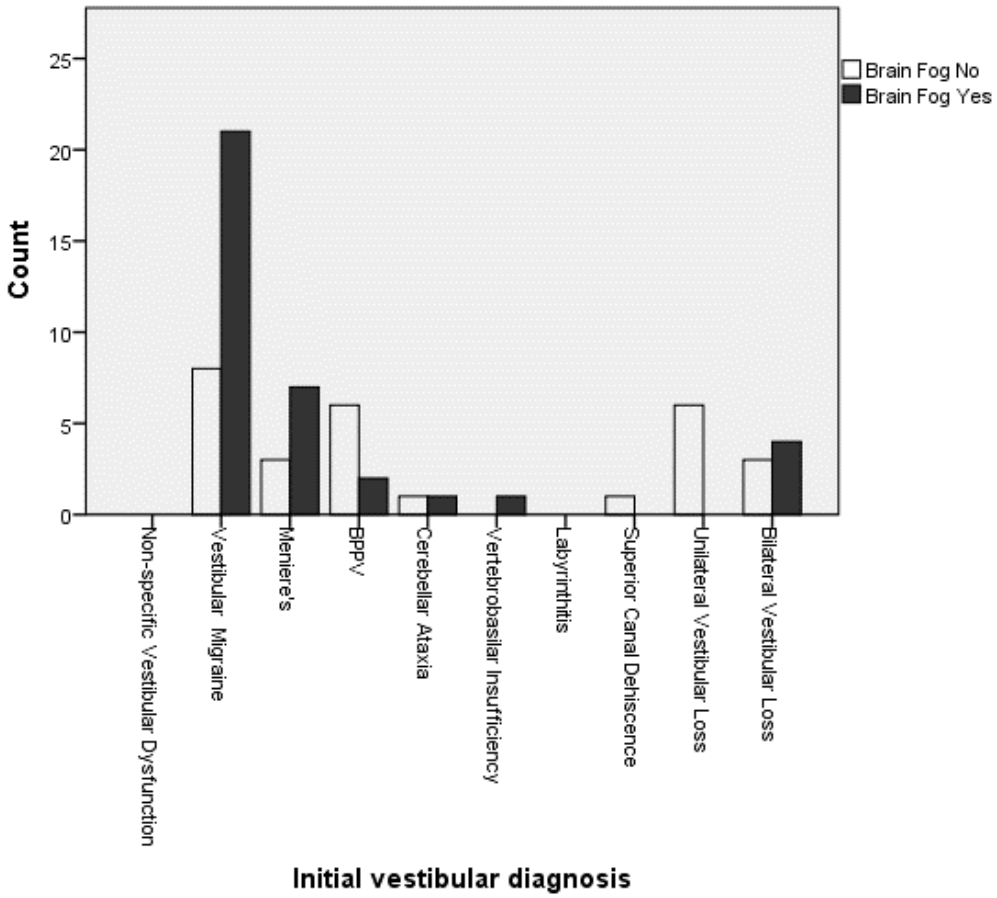

Figure 1. Count of participants' initial vestibular diagnoses by fogginess

Given that the diagnosis of vestibular migraine (VM) was present in both groups, the initial vestibular diagnosis variable was divided into VM and other categories. Count for each group by brain fog is presented in Figure 2. Chi-square test was performed to evaluate the strength of the relationship between brain fog presence and vestibular diagnosis. There was significant association between initial vestibular diagnosis and whether the participant had brain fog or not ($\chi^2(1) = 4.69$, $p = .027$, $\varphi_c = .26$), indicating a moderately strong association. Visual examination of figure indicated that the difference in the number of individuals with VM and other vestibular diagnoses was significantly larger for the Brain Fog No group compared to the Brain Fog Yes group.

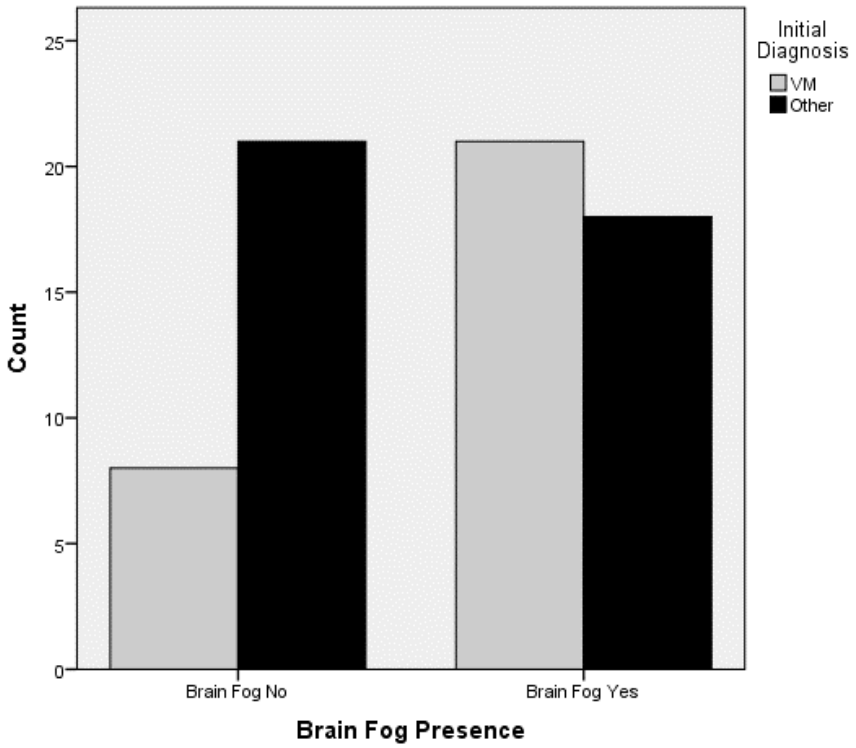

Figure 2. Count of initial diagnosis of VM and other disorders by brain fogginess

Point-biserial correlations were calculated to determine the relationship between the report of brain fogginess and the total scores of various questionnaires, Patient Health Questionnaire (PHQ-9), Somatic Symptom Scale (SSS-8), General Anxiety Disorder 7-item (GAD7), and Health Anxiety Inventory Short Form (HAI-S), used to evaluate psychiatric well-being of the study participants (Table 2). There was a strong, positive statistically significant correlation between brain fog and PHQ-9 ($r_{pb}(67) = .374$, $p = .002$), SSS-8 ($r_{pb}(67) = .446$, $p < .001$), GAD-7 ($r_{pb}(66) = .299$, $p = .014$), HAI-S ($r_{pb}(67) = .357$, $p = .003$) indicating that participants with higher total score on each questionnaire would be more likely to report having brain fog compared to those with lower scores.

Table 2

Relationship between Brian Fogginess with Psychiatric Well-Being Questionnaires.

Questionnaires	Brain Fogginess		
	N	Point-Biserial Correlation	*Sig*. (2-tailed)
PHQ-9	68	.374	.002
SSS-8	68	.446	<.001
GAD-7	67	.299	.014
HAI-S	68	.357	.003

Mean scores of the diagnostic questionnaires by brain fogginess are presented in Figure 3 and Table 3. Independent sample *t*-tests indicated that Brain Fog Yes group had significantly higher scores relative to Brain Fog No group for all 4 questionnaires: PHQ-9 ($t(66) = 3.277$, $p = .002$, $r = .387$, corresponding to large effect size), SSS-8 ($t(66) = 4.046$, $p < .001$, $r = .453$, corresponding to large effect size), GAD-7 ($t(65) = 2.528$, $p = .014$, $r = .306$, corresponding to large effect size), HAI-S ($t(66) = 3.106$, $p = .003$, $r = .363$, corresponding to large effect size).

Table 3

Mean Scores of Diagnostic Questionnaires by Brain Fog Presence

	Sample			*p*-value	Effect Size (*r*)
	Overall (N = 67)	Brain Fog Yes (N = 39)	Brain Fog No (N = 29)		
Questionnaire	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*		
PHQ-9	7.31 (6.48)	9.39 (7.28)	4.52 (3.82)	.002	.387
SSS-8	10.53 (5.55)	12.65 (5.64)	7.69 (3.97)	<.001	.453
GAD-7	5.22 (5.63)	6.64 (6.06)	3.25 (4.34)	.014	.306
HAI-S	12.14 (6.57)	14.15 (6.93)	9.45 (4.98)	.003	.363

Figure A

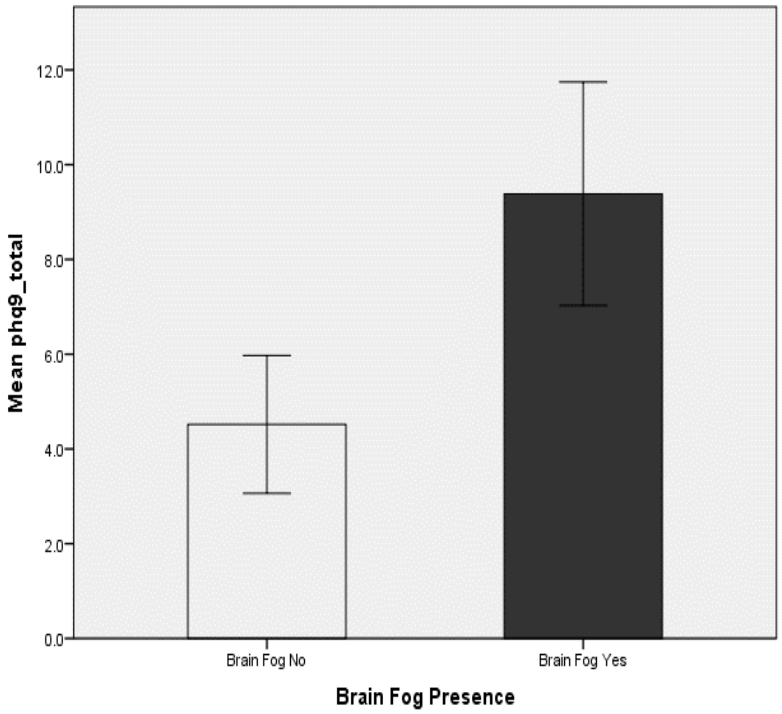

Figure B

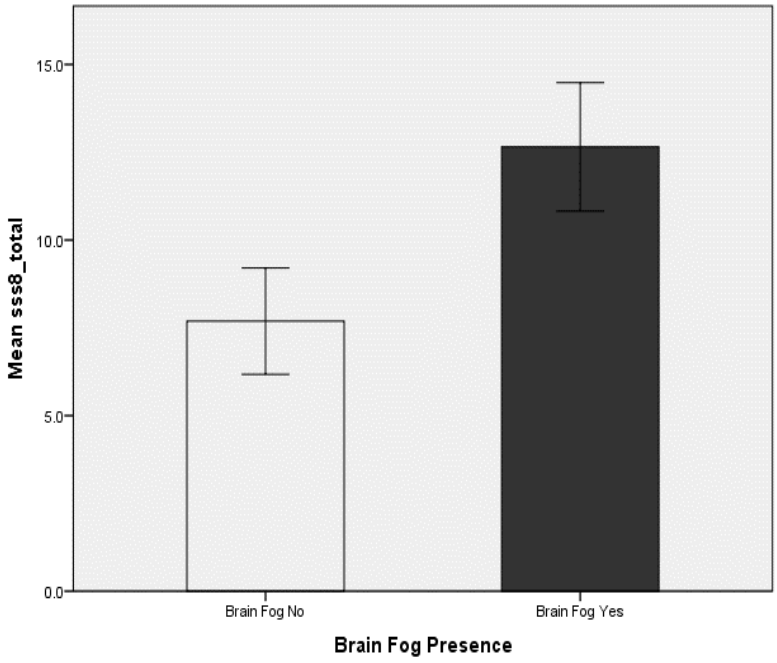

Figure C

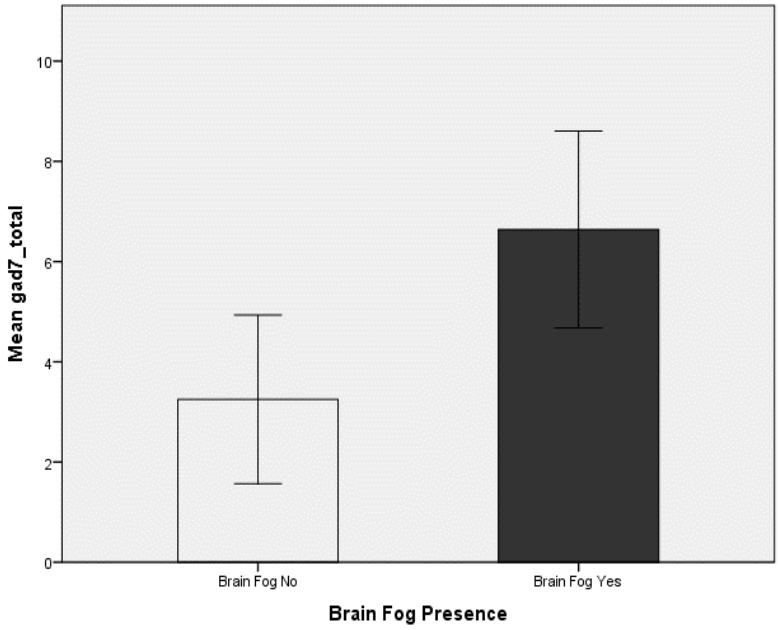

Figure D

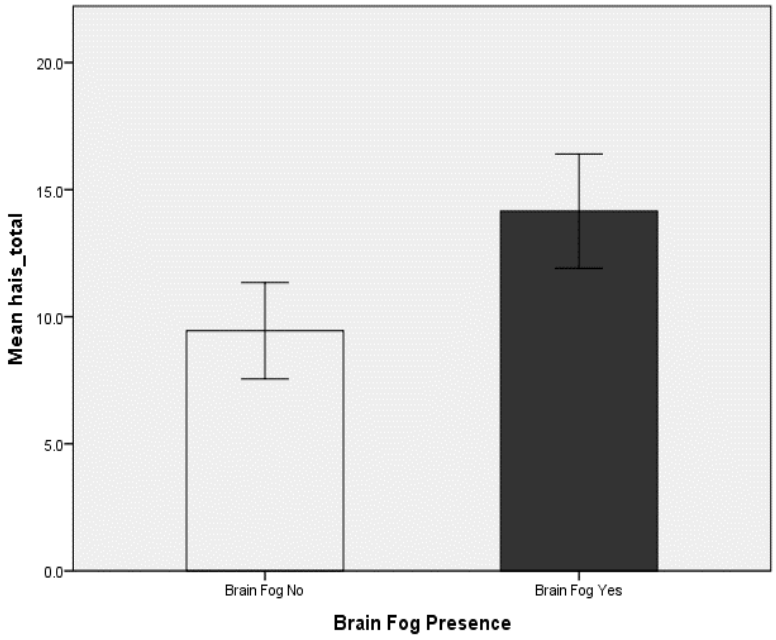

Figure 3. Mean scores of the diagnostic questionnaires for the two groups: A) PHQ-9; B) SSS-8; C) GAD-7; D) HAI-S. Error bars represent CI = 95% around the mean for all 4 graphs.

Descriptive Results of Brain Fog Scale

Cognitive Disturbance Scale was administered to obtain descriptive characteristics of brain fog. A Brain Fog Severity variable was created by computing the average score of 21 symptoms presented in the scale. Table 4 below has the mean severity of each symptom and the prevalence among the group. Based on these outcomes, the most commonly-occurring symptoms were difficulty focusing (72.5%), slow (72.5%), forgetful (67.5%), difficulty thinking (67.5%), and exhausted (65). The least-reported symptoms were difficulty finding your way (25%) and lost (20%). Difficulty focusing (45.13), slow (40), difficulty thinking (36.28) and exhausted (36.03) had the highest mean severity score while lost (10.25) and difficulty finding your way (8.16) had the lowest.

Regression Analyses

Linear regression analyses with brain fog severity as dependent variable were applied to diagnostic questionnaires. Age and sex were controlled for. Results are reported in Table 5.

Hierarchical multiple linear regression was performed to investigate the ability of initial vestibular diagnosis in predicting brain fog severity, after controlling for age and gender. The model predicting brain fog severity with age and sex as predictors was statistically significant ($F(2, 37) = 3.43$; $p = .043$) and accounted for 16% of the variance in brain fog severity. Initial vestibular diagnosis accounted for an additional 0.2% of the variance in brain fog severity, after controlling for age and sex (R^2 Change = .002; $F(3,36) = 2.27$, $p = .097$)

Hierarchical multiple linear regression was performed to investigate the ability of PHQ-9 questionnaire score in predicting brain fog severity, after controlling for age and gender. PHQ-9 score accounted for an additional 18% of variance in brain fog severity, after controlling for age and sex (R^2 Change = .18, $F(3, 36) = 6.15$, $p = .002$). In the final adjusted model two out of three predictor variables were statistically significant, with PHQ-9 recording a higher Beta value ($\beta = .43$, $p = .003$) than sex ($\beta = -.33$, $p = .022$).

Table 4

Brain Fog Descriptors Based on Cognitive Disturbance Scale

Symptoms	% of People with Symptom (n = 29)	Symptom Mean (SD)
confusion	62.5	26.54 (32.24)
easily distracted	52.5	28.5 (34.0)
forgetful	67.5	31.25 (31.78)
annoying	52.5	23.13 (30.23)
exhausted	65.0	36.03 (35.28)
slow	72.5	40 (34.21)
cloudy	52.5	32.05 (36.32)
spacey	57.5	35.75 (35.82)
sleepy	56.4	27.5 (32.50)
lost	20.0	10.25 (23.78)
detached	40.0	21.63 (34.31)
thoughts moving quickly	35.7	17.63 (29.20)
mind went blank	62.5	33.75 (36.00)
mental fatigue	50.0	25.92 (34.10)
difficulty focusing	72.5	45.13 (35.29)
difficulty thinking	67.5	36.28 (35.01)
difficulty finding right words	60.0	33.75 (35.82)
difficulty processing what others say	45.0	20.26 (30.91)
difficulty processing words read	42.5	20.5 (29.48)
difficulty finding your way	25.0	8.16 (21.76)
trouble driving	40.0	18.08 (31.13)

Table 5

Multiple Linear Regression Analysis with Brain Fog Severity as Dependent Variable Controlling for Age and Sex

	M	*SD*	*N*	Correlation with Brain Fog	Multiple Regression Weight *b*	*B*	*p*-value	R^2 Change
IVD			40	-.024	2.03	.05	.754	.002
PHQ-9	9.20	7.28	40	.449*	1.19	.43	.003	.182
SSS-8	12.49	5.67	40	.602**	2.12	.59	<.001	.35
GAD-7	6.58	6.0	40	.518**	1.72	.51	<.001	.252
HAI-S	14.05	6.87	40	.089	.68	.23	.151	.048

Note. IVD = initial vestibular diagnosis; * = correlation is significant at the .05 level (1-tailed);

** = correlation is significant at the .001 level (1-tailed)

Hierarchical multiple linear regression was performed to investigate the ability of SSS-8 questionnaire score in predicting brain fog severity, after controlling for age and gender. SSS-8 score accounted for an additional 35% of variance in brain fog severity, after controlling for age and sex (R^2 Change = .35, $F(3, 36) = 12.30$, $p < .001$). In the final adjusted model two out of three predictor variables were statistically significant, with SSS-8 recording a higher Beta value ($\beta = .59$, $p < .001$) than sex ($\beta = -.34$, $p = .007$).

Hierarchical multiple linear regression was performed to investigate the ability of GAD-7 questionnaire score in predicting brain fog severity, after controlling for age and gender. GAD-7 score accounted for an additional 25% of variance in brain fog severity, after controlling for age and sex (R^2 Change = .25, $F(3, 36) = 8.29$, $p < .001$). In the final adjusted model two out of three predictor variables were statistically significant, with GAD-7 recording a higher Beta value ($\beta = .51$, $p < .001$) than sex ($\beta = -.35$, $p = .009$).

Hierarchical multiple linear regression was performed to investigate the ability of HAI-S questionnaire score in predicting brain fog severity, after controlling for age and gender. HAI-S score accounted for an additional 5% of variance in brain fog severity, after controlling for age and sex (R^2 Change = .05, $F(3, 36) = 3.08$, $p = .04$). In the final adjusted model, only sex, out of three predictor variables, was statistically significant, recording Beta value ($\beta = -.40$, $p = .013$).

Pearson product-moment correlations were calculated to determine the relationship between brain fog severity and initial vestibular diagnosis, controlling for age, gender, PHQ-9, and HAI-S. Table 6 summarizes the descriptive statistics and analysis results. It can be seen that PHQ-9 is positively and significantly correlated with brain fog severity, indicating that individuals with higher PHQ-9 score had higher brain

for severity. Also, there was a significant negative correlation between sex and brain fog severity indicating that females have less brain severity than males.

Table 6

Multiple Linear Regression Analysis with Brain Fog Severity as Dependent Variable Controlling for Age, Sex, PHQ-9, and HAI-S Total Scores

	M	*SD*	*N*	Correlation with Brain Fog	*β*	*p*-value
IVD			40	-.024	-.015	.925
Age	54.45	12. 680	40	-.20	-.174	.247
Sex			40	-.34*	-.323	.037
PHQ-9	9.20	7.280	40	.449*	.433	.013
HAI-S	14.05	6.872	40	.089	-.007	.972

Note. IVD = initial vestibular diagnosis; * = correlation is significant at the .05 level (1-tailed).

Hierarchical multiple linear regression was performed to investigate the ability of initial vestibular diagnosis in predicting brain fog severity, after controlling for age, sex, PHQ-9, and HAI-S. The model predicting brain fog severity with age, sex, PHQ-9, and HAI-S as predictors was statistically significant ($F(4, 35) = 4.49$; $p = .005$) and accounted for 34% of the variance in brain fog severity. Initial vestibular diagnosis did not introduce additional explanation of variance in brain fog severity, after controlling for age, sex, PHQ-9, and HAI-S, (R^2 Change = 0; $F(5, 34) = 3.49$; $p = .012$). In the final adjusted model two out of five predictor variables were statistically significant, with PHQ-9 recording a higher Beta value ($\beta = .433$, $p = .013$) than sex ($\beta = -.32$, $p = .037$).

A series of logistic regression analyses were performed to investigate the relationship between brain fog presence and its possible predictors: initial vestibular diagnosis, PHQ-9, SSS-8, GAD-7, and HAI-S after controlling for participant's sex and age. Table 7 shows the logistic regression coefficient, Wald test, significance, odds ratio,

and percent correct classification for each of the predictors. From table 7, it is evident that PHQ-9, SSS-8, and HAI-S were significant predictors of brain fog presence after controlling for the effect of age and sex.

Table 7

Logistic Regression Analysis Predicting Brain Fog from Possible Predictors after Controlling for the Effect of Age and Sex

Predictor	*B*	Wald χ^2	*p*-value	Odds ratio	% correct classification
IVD	-.86	2.39	.122	.424	67.2
PHQ-9	.16	6.98	.008	1.172	71.6
SSS-8	.24	10.65	.001	1.265	73.1
GAD-7	.11	3.35	.067	1.118	72.7
HAI-S	.14	7.15	.007	1.144	70.1

Note. IVD = initial vestibular diagnosis

The multiple logistic regression model predicting brain fog presence with age and sex as predictors was not statistically significant ($\chi^2(2) = 3.69$; $p = .158$) and accounted for 7% (Nagelkerke R^2) of the variance in brain fog presence. PHQ-9 questionnaire score accounted for an additional 18% (Nagelkerke R^2) of the variance in brain fog presence, after controlling for age and sex ($\chi^2(3) = 13.565$; $p = .004$). For every one-point increase in PHQ-9 questionnaire score, we expect a 17% increase in brain fog presence, holding all other variables at constant.

Hierarchical multiple logistic regression was performed to investigate the ability of SSS-8 questionnaire score in predicting brain fog presence, after controlling for age and gender. SSS-8 score accounted for an additional 26% (Nagelkerke R^2) of the variance in brain fog presence, after controlling for age and sex ($\chi^2(3) = 19.172$; $p < .001$). In the final adjusted model two out of three predictor variables were statistically significant,

with SSS-8 having a higher odds ratio (B = .24, p = .001) than age (B = -.05, p = .031). For every one-point increase in SSS-8 questionnaire score, we expect a 27% increase in brain fog presence, holding all other variables at constant.

Hierarchical multiple logistic regression was performed to investigate the ability of HAI-S questionnaire score in predicting brain fog presence, after controlling for age and gender. HAI-S score accounted for an additional 16% (Nagelkerke R^2) of the variance in brain fog presence, after controlling for age and sex ($\chi^2(3) = 12.476$; p = .006). For every one-point increase in HAI-S questionnaire score, we expect a 14% increase in brain fog presence, holding all other variables at constant.

Table 8

Multiple Logistic Regression Analysis Predicting Brain Fog from Possible Predictors after Controlling for Age, Sex, PHQ-9, and HAI-S Total Scores

Predictor	*B*	Wald χ^2	*p*-value	Odds ratio
VM	-1.30	3.95	.047	.272
Age	-.03	1.55	.213	.973
Sex	-.04	.004	.948	.959
PHQ-9	.12	3.18	.075	1.125
HAI-S	.136	5.11	.024	1.145

Multiple logistic regression analysis was performed to predict the probability that a participant would have brain fog based on the initial vestibular diagnosis after controlling for age, sex, PHQ-9 and HAI-S. The resulting model was significant ($\chi^2(5) = 21.94$; p = .001) and accounted for 38% (Nagelkerke R^2) of the variance in brain fog presence and had an overall success rate of 80.6% in correctly classifying the presence of brain fog. Table 8 shows the logistic regression coefficient, Wald test statistics, and odds

ratio for each of the predictors. The odds of individuals having brain fog with an initial diagnosis of VM are 37% higher than the odds of having brain fog with other diagnoses.

CHAPTER 5: DISCUSSION

The discussion section will be organized in a manner answering the research questions and goals of the current study. First, brain fog and its manifestation in patients based on the study findings will be discussed. Then, the psychiatric confounders of the phenomenon will be addressed. Lastly, the underlying causes of brain fog will be discussed.

Brain Fog Description

Brain Fog Demographics

The study included participants of both sexes, ages 22 – 85 years old. The racial composition included white, black, and participants identified as others. Based on the presence of brain fog report, Brain Fog Yes and Brain Fog No groups were established. No significant difference was noted between the means of two groups for age, sex, and race indicating that brain fog presence was not affected by those factors. The outcomes of the multiple linear regression used to examine the relationship between brain fog severity and age, gender, PHQ-9, and HAI-S, however, revealed that the manifestation of the brain fog symptoms is less severe in females compared to males.

Brain Fog Symptoms and Severity

The participants who confirmed having brain fog were asked to complete Cognitive Disturbance Scale, in an attempt to understand the essence of the phenomenon. Based on the outcomes, “difficulty focusing” and “slow” were the most reported symptoms of brain fog, followed by “difficulty thinking” and “forgetful”. “Exhausted” was the third most common symptom of the phenomenon. “Confusion” and “mind went blank” were the fourth, and “difficulty finding right words” was the fifth most commonly-occurring symptom. These findings are consistent with the literature. The

study of Ross and colleagues (2013) found that “forgetful” was the most prevalent complaint among the participants of their study (*n* = 138) that investigated brain fog in people with Postural Orthostatic Tachycardia Syndrome (POTS). “Difficulty thinking” was second and “difficulty focusing”, “cloudy”, and “difficulty finding right words/communicating” were the third most common symptoms. “Mental fatigue” and “slow” followed by “mind went blank” concluded the top 5 most frequently-used descriptors of brain fog. The authors claimed that the top ranking of such descriptors as “forgetful”, “difficulty thinking”, “difficulty focusing”, “and difficulty finding right words/communicating” is indicative of impaired cognition (Ross et al., 2013). In another study, Wise et al. (2017) stated that “forgetful” was the primary complaint of their study participants (*n* = 135) with brain fog. “Cloudy”, “spacey”, “difficulty focusing”, “difficulty thinking” and “difficulty finding right words” were given the second place, followed by “exhausted”, “slow”, and “mental fatigue.” The current study findings also indicate that “difficulty focusing”, “slow”, “difficulty thinking”, “exhausted”, and “spacey” were the most severe symptoms experienced by the participants of this study. The difference in the ranking of the descriptors of brain fog may be explained by the difference in the sample size, with the current study being significantly smaller (*n* = 68) compared to those of Ross et al. (2013) and Wise et al. (2017). Additionally, those studies examined patients with POTS while this study concentrated on participants with various vestibular diagnoses.

Psychiatric Confounders

All of the study participants had to fill out Patient Health Questionnaire (PHQ-9), Somatic Symptom Scale (SSS-8), General Anxiety Disorder 7-item (GAD7), and Health Anxiety Inventory Short Form (HAI-S), screening for depression, somatic symptoms burden, anxiety, and hypochondriasis, respectfully. Ocon (2013) stated that psychiatric diseases do not seem to be related to brain fog. Our findings, on the other hand, established statistically significant strong positive correlations between all 4 questionnaires and brain fog presence, indicating that participants with higher total scores would be more likely to have brain fog compared to those with lower scores. These results were consistent with the outcomes of independent *t*-test comparing means of Brain Fog Yes and Brain Fog No groups. The outcomes of hierarchical multiple regression indicated that PHQ-9, SSS-8, and GAD-7 are effective in predicting brain fog severity, after controlling for age and sex. Multiple hierarchical logistic regression models indicated that PHQ-9, SSS-8, and HAI-S were significant predictors of brain fog presence, after controlling for the effect of age and sex. Based on these findings, we can conclude that depression and somatic symptoms burden predict brain fog severity and brain fog presence. However, anxiety accounts for unique variance in predicting brain fog severity whereas hypochondriasis accounts for unique variance in predicting brain fog presence.

Underlying Causes of Brain Fog

Earlier in the study, the relationship between vestibular dysfunctions and affective disorders, including depression and anxiety was discussed. Parallel to establishing a connection between the psychiatric conditions and brain fog, possible relationships

between initial vestibular diagnosis and the phenomenon were investigated. A strong negative correlation was observed between vestibular diagnoses and brain fog. Specifically, it appears that patients with vestibular migraine (VM) are more likely to have brain fog than those diagnosed with bilateral vestibular disorders. Additionally, multiple logistic regression indicated that the odds of individuals having brain fog with an initial diagnosis of VM are 37% higher than the odds of having brain fog with other diagnoses. In the multiple linear regression model, however, initial vestibular diagnosis did not introduce an additional explanation of variance in brain fog severity, after controlling for age and sex.

Chen (2013) discussed brain fog from the perspective of the personal experience of chronic migraines. He described brain fog as "feeling stupid" or inability to think ("can't think"), consistent with the descriptors from this study. Considering that the diagnostic criteria for vestibular migraine require a current/present history of migraines, according to the International Headache Association (Stolte, Holle, Naegel, Diener, & Obermann, 2015), his description of brain fog is not surprising. Several studies also implicated that those with vestibular migraines are very likely to present with comorbid conditions, such as anxiety, panic disorders, and clinical depression (O'Connell Ferster, Priesol, & Isildak, 2017; Stolte et al., 2015). According to Eckhardt-Henn (2008), as many as 65% of patients with vestibular migraine would present with anxiety and depressive disorders. Following the statement of Odman and Maire (2008) that somatopsychic pathologies have vestibular causes, it is concluded that an underlying vestibular condition is, indeed, resulting in a psychiatric disorder that then manifests in the patient experiencing brain fog.

Study Limitations

There are several limitations of the current study. First, the outcomes of the study could have been affected by the fact that almost 43% of the study participants (n = 29) had an initial diagnosis of VM. Despite 9 different diagnoses categories being included in the study, the distribution of the participants among them was not equal. “Non-specific vestibular dysfunction” and “labyrinthitis” categories had no study participants affiliated with them.

Secondly, even though no significant difference was noted between the means of Brain Fog Yes and Brain Fog No groups for race, the dominant part of the study participants was white. Recruitment of a more diverse study sample could have yielded different outcomes.

Lastly, data logging was another limitation of this study (sex, race, and gender of 1 participant from Brain Fog No group were un known, as well as initial diagnoses of 4 other study members). There were several instances where participants’ information was missing from the data log across multiple categories.

Future Research

Based on the limitations of the current study, several suggestions for future research can be made. First, this study has shown that brain fog is a common condition among people suffering from various vestibular dysfunctions. However, considering that most of the initial vestibular diagnosis categories were underrepresented, it would be beneficial to examine the odds of other vestibular pathologies, besides VM, to predict brain fog, with an equal number of participants across the diagnoses in a larger study

sample. Secondly, it would also be interesting to evaluate effect of race on brain fog prediction in a multiple regression model, in a more diverse study sample.

Finally, research of alleviating factors of brain fog in patients with vestibular dysfunction is necessary. Ross et al. (2013) stated that a high sodium diet and increased caffeine intake improve brain fog symptoms in patients with POTS. Such treatment, however, would be contraindicative for patients with VM and MD (Stolte et al., 2015). Wise and colleagues (2017) reported that some POTS patients with brain fog reported decrease of physical activity to be beneficial in their symptoms alleviation. Physical activity of daily living (walking, sitting down, etc.), on the other hand, is essential for patients with uncompensated vestibular weakness, in order for central compensation to occur (Barin, 2016).

APPENDIX A

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

APPENDIX B

The Somatic Symptom Scale-8 (SSS-8)

During the past 7 days, how much have you been bothered by any of the following problems?

1. Stomach or bowel problems
    A. Not at all (0)
    B. A little bit (1)
    C. Somewhat (2)
    D. Quite a bit (3)
    E. Very much (4)
2. Back pain
    a. Not at all (0)
    b. A little bit (1)
    c. Somewhat (2)
    d. Quite a bit (3)
    e. Very much (4)
3. Pain in your arms, legs, or joints
    a. Not at all (0)
    b. A little bit (1)
    c. Somewhat (2)
    d. Quite a bit (3)
    e. Very much (4)
4. Headaches
    a. Not at all (0)
    b. A little bit (1)
    c. Somewhat (2)
    d. Quite a bit (3)
    e. Very much (4)
5. Chest pain or shortness of breath
    a. Not at all (0)
    b. A little bit (1)
    c. Somewhat (2)
    d. Quite a bit (3)
    e. Very much (4)
6. Dizziness
    a. Not at all (0)
    b. A little bit (1)
    c. Somewhat (2)
    d. Quite a bit (3)
    e. Very much (4)
7. Feeling tired or having low energy
    a. Not at all (0)
    b. A little bit (1)
    c. Somewhat (2)
    d. Quite a bit (3)
    e. Very much (4)
8. Trouble sleeping
    a. Not at all (0)
    b. A little bit (1)
    c. Somewhat (2)
    d. Quite a bit (3)
    e. Very much (4)

Glerk B, Kohlmann S, Kroenke K, Spanenberg L, Zenger M, Brahler E, Lowe B. The Somatic Symptom Scale-8 (SSS-8) A Brief Measure of Somatic Symptom Burden. JAMA Intern Med. 2014: 174(3): 399-407.

APPENDIX C

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Intern Med.* 2006;166:1092-1097.

APPENDIX D

Health Anxiety Inventory – Short Form (HAI-S)

Each question in this section contains a group of four statements. Please read each group of statements and circle the letter of the one that best describes you over the last six months. If more than one statement fits, circle all the letters that apply to you.

1. I worry about my health

   A. Never, not at all
   B. Occasionally
   C. Much of the time
   D. Most of the time

2. I notice aches and pains

   A. Less than most people my age
   B. As much as most people my age
   C. More than most people my age
   D. All of the time

3. I am aware of bodily sensation or changes

   A. Never, not at all
   B. Occasionally
   C. Much of the time
   D. Most of the time

4. Regarding thoughts of illness

   A. I can resist them with no problem.
   B. I can resist them most of the time.
   C. I try to resist them, but often cannot do it.
   D. I do not try to resist them, because they are so strong.

5. I am afraid that I have a serious illness

   A. Never, not at all
   B. Occasionally
   C. Much of the time
   D. Most of the time

6. I have mental images of myself being ill

   A. Never, not at all
   B. Occasionally
   C. Much of the time
   D. Most of the time

7. Regarding thoughts about my health

   A. I have no difficulty with them.
   B. I sometimes have difficulty taking my mind off them.
   C. I often have difficulty taking my mind off them.
   D. Nothing can take my mind off them.

8. If my doctor tells me that there is nothing wrong with my health,

   A. I am completely relieved.
   B. I am relieved at first, but worries sometimes return later.
   C. I am relieved at first, but worries always return later.
   D. I am not relieved at all.

9. If I hear about an illness,

   A. I never think that I have it myself.
   B. I sometimes think that I have it myself.
   C. I often think that I have it myself.
   D. I always think that I have it myself.

Health Anxiety Inventory – Short Form (HAI-S)

Each question in this section contains a group of four statements. Please read each group of statements and circle the letter of the one that best describes you over the last six months. If more than one statement fits, circle all the letters that apply to you.

10. If I have a body sensation or change,

    A. I rarely wonder what it means.
    B. I often wonder what it means.
    C. I always wonder what it means.
    D. I have to know what it means.

11. I feel that my risk for developing a serious illness is

    A. Very low
    B. Fairly low
    C. Moderate
    D. High

12. I believe that I have a serious illness

    A. Never, not at all
    B. Occasionally
    C. Much of the time
    D. Most of the time

13. If I notice a body sensation that I cannot explain,

    A. I don't find it difficult to think of other things.
    B. I sometimes find it difficult to think of other things.
    C. I often find it difficult to think of other things.
    D. I always find it difficult to think of other things.

14. My family members and friends would say that

    A. I do not worry enough about my health.
    B. I have a normal attitude about my health.
    C. I worry too much about my health.
    D. I am a hypochondriac.

Reformatted from: P. M. SALKOVSKIS, K. A. RIMES, H.M. C. WARWICK and D.M. CLARK. The Health Anxiety Inventory: development and validation of scales for the measurement of health anxiety and hypochondriasis. *Psychological Medicine*, 2002, 32:843-853. Cambridge University Press

APPENDIX E

Cognitive Disturbance

1. Since you began to experience dizziness, have you felt mentally dully, "foggy", or cannot think as clearly as you used to?
   a. No, please skip this questionnaire
   b. Yes
2. If you answer "Yes" above, fill out this table:

When you felt "foggy", did you experience:	**Yes** Put "X" if it applies to you	**How well does this symptom describe you when you feel "foggy"?** On a scale of 0-100, indicate how you severe the problem is for you. The higher the number, the more severe the problem. You can mark anywhere along the scale.	**How often does this happen?** 0=very infrequent 1=infrequent 2=neutral 3=somewhat frequent 4=very frequent	**What time of the day do you experience this?** 0=morning 1=afternoon 2=evening 3=middle of the night 4=It changes/ is variable
Example: sample	x	0 10 20 30 40 50 60 70 X 80 90 100	0 1 2 (3) 4	0 1 2 3 (4)
Confusion		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Easily distracted		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Forgetful		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Annoying		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Exhausted		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Slow		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Cloudy		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Spacey		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Sleepy		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Lost		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Detached		0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4

Thoughts moving quickly		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Mind went blank		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Mental fatigue		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Difficulty focusing		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Difficulty thinking		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Difficulty finding right words		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Difficulty processing what others say		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Difficulty processing words read		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Difficulty finding your way		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4
Trouble driving		----|----|----|----|----|----|----|----|----|----| 0 10 20 30 40 50 60 70 80 90 100	0 1 2 3 4	0 1 2 3 4

APPENDIX F

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **Longitudinal tracking of balance and falls**

Application No.: **NA_00087648**

Sponsor: **National Institutes of Health**

Principal Investigator: **Yuri Agrawal, M.D.**
Associate Professor, Division of Otology, Neurotology and Skull Base Surgery
Department of Otolaryngology-Head & Neck Surgery
Johns Hopkins University School of Medicine
601 N. Caroline St., 6th Floor
Clinical Office: 410-502-3107
Research Office: 410-614-5902
Fax: 410-955-0035

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1. What you should know about this study:

- You are being asked to join a research study. This consent form explains the research study and your part in it. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information that you do not understand.
- You are a volunteer. If you join the study, you can change your mind later. There will be no penalty or loss of benefits if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.
- If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout Johns Hopkins. Doctors outside of Johns Hopkins may not have access to this information. You can ask the research team to send this information to any of your doctors.
- When Johns Hopkins is used in this consent form, it includes The Johns Hopkins University, The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Johns Hopkins Community Physicians, Suburban Hospital, Sibley Memorial Hospital and All Children's Hospital.

2. Why is this research being done?

This research is being done to better understand why falls and/or balance disorders occur in older adults, and how falls impact the lives of older adults.

Falls are commonly the result of multiple factors, including problems related to the visual, balance, musculoskeletal, and neurological systems. As a participant of this study, we will evaluate multiple factors that may contribute to falls. We plan to include the results of your evaluation in a falls clinic database to be used in future research studies to better understand the different risk factors for falls and investigate different interventions to reduce fall risk in older adults.

How many people will be in this study?

About 250 people are expected to participate.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things that are checked, "Yes.":

___ Yes ___ No HISTORY AND PHYSICAL EXAMINATION

A faculty, fellow or resident doctor will perform a history and clinical examination. You will also be asked to complete some questionnaires.

___ Yes ___ No LIGHTWEIGHT VIDEO GOGGLES EYE MOVEMENT TESTING

We will measure your eye movements with lightweight video goggles. This is a noninvasive procedure that allows accurate eye movement recordings without any eye discomfort. We will move your head by hand.

___ Yes ___ No VEMP (VESTIBULAR-EVOKED MYOGENIC POTENTIALS)

We will play tones to your ear and use skin-pad electrodes to record neck muscle activity while you rest in a chair and turn your heads lightly for about 1 minute at a time. We will perform VEMP testing while you are sitting upright.

We may also record muscle activity around the eyes. We may stimulate the balance reflexes with gentle taps on the head. The electrical current can cause a brief tingling sensation and a sense of imbalance.

___ Yes ___ No HEARING TEST

A trained study team member will ask you whether you hear sounds and spoken words played through a speaker over or behind your ear. With an ear plug placed temporarily in your ear canal, a tone plays through a speaker while light pressure is applied to your ear. These tests take about 15-20 minutes.

___ Yes ___ No COGNITIVE TESTS
We will ask you to complete several cognitive function tests. These tests will assess things like your memory or ability to complete a maze. Testing will be performed while seated using pen and paper or a computer.

___ Yes ___ No NAVIGATION TASK
We will ask you to walk in a series of patterns in an open room (i.e. square, circle, triangle). We will ask you to walk first with your eyes open, then with a blindfold. The examiner will be with you at all times to minimize any risk of imbalance or falls.

___ Yes ___ No BALANCE AND GAIT ASSESSMENT
We will ask you to keep your balance while standing under different conditions (e.g. feet together, with head turn) and we will also ask you to walk over a prescribed path. This will take about 5 minutes. We may also ask you to wear some small sensors with Velcro straps to measure your walking.

___ Yes ___ No VISION TESTING
We will evaluate your vision. This may include a history, external eye assessment, static visual acuity, and peripheral vision.

___ Yes ___ No FRAILITY EXAMINATION
We will ask you to complete a walk speed test and grip strength test.

___ Yes ___ No MONTHLY FOLLOW-UP FOR TWO YEARS
We would like you to keep a record of any falls you may have for two years. We will provide you with a calendar with boxes to check off and/or we will call you every three months over the follow-up period, and/or we will use a text messaging system to track your falls. We may also ask you to wear a small sensor to measure your physical activity for a week.

___ A SINGLE TESTING SESSION ___ MULTIPLE TESTING SESSIONS
We will review your test results with you, and we will give them to your doctor if you request. The data we collect will be kept in a secure research database.

How long will you be in the study?
Information about you will be in the database for the duration that the study protocol is active.

4. What are the risks or discomforts of the study?

There are no medical risks directly associated with the creation and maintenance of the falls clinic database.

Although head movements in the test performed stay within the comfortable range you demonstrate to us beforehand, rapid head movements could cause neck

injury or soreness. If an injury occurs, a study team member will evaluate and treat you.

Although unlikely, you may fall during the navigation task. The examiner will be with you at all times to stabilize you should you become unsteady.

You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.

There is a risk for the loss of confidentiality. To address this risk, the database is password protected and accessible only to approved members of the study team. Any paper-based records will be stored in locked cabinets of the Dept. of Otolaryngology in the Johns Hopkins Outpatient Center.

5. Are there benefits to being in the study?

There is no direct benefit to you from being in this study. Your participation in this study will help us better understand the risk factors and causes of falls, which may lead to better clinical evaluation and management strategies for people at risk for falls. Your participation may influence how diagnostic and therapeutic measures are carried out in the future.

6. What are your options if you do not want to be in the study?

You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected.

7. Will it cost you anything to be in this study?

No.

8. Will you be paid if you join this study?

Yes.

Participants may receive up to $100 total for participating in the study; $20 for the first, baseline visit, $30 for a 1 year follow up visit, and $50 for a 2 year follow up visit.

You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from Johns Hopkins exceed $600 per year, Johns Hopkins will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form from us.

9. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities**.**

10. Why might we take you out of the study early?

You may be taken out of the study if you choose not to seek care in the Johns Hopkins Falls Prevention Clinic.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that it already has if the information is needed for this study or any follow-up activities**.**

11. How will your privacy be protected?

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records (which may include information about HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Information will be collected from you as part of your evaluation at the Falls Prevention Clinic. This includes things learned from your medical history and physical exam as well as other information including your name, address, date of birth, and fall history.

Any paper-based patient records will be stored in locked cabinets in the Dept. of Otolaryngology on the 6th floor of the Johns Hopkins Outpatient Center. The study database will be password protected with password access limited to the PI and co-investigators authorized by the IRB. This password will not be shared with non-authorized personnel. All audio files of interviews will be stored as MP3 files and saved on a secure computer with password protection. Audio files will be transferred to the secure computer and deleted from the digital recorder within 3 days after the corresponding interview is conducted. Transcripts from the interviews will be redacted to remove any personally-identifying information prior to analysis.

The research team will know your identity and that you are in the research study. Other people at Johns Hopkins, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety.

People outside of Johns Hopkins may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study.

If you are in a cancer study that receives federal funding, the National Cancer Institute (NCI) now requires that we report identifiable information (such as, zip code) about your participation. You may contact the NCI if you have questions about how this information is used.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

12. Will the study require any of your other health care providers to share your health information with the researchers of this study?

No.

13. What if there is a Certificate of Confidentiality for this study?

Your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing

your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

14. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The Johns Hopkins Medicine IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

When the Johns Hopkins School of Medicine Institutional Review Board (IRB) reviews a study at another site, that site (institution) is solely responsible for the safe conduct of the study and for following the protocol approved by the Johns Hopkins IRB.

b. What do you do if you have questions about the study?

Call the study doctor, Dr. Yuri Agrawal at 410-502-3107. If you wish, you may contact the study doctor by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What happens to Data that are collected in the study?

Johns Hopkins and our research partners work to understand and cure diseases. The data you provide are important to this effort.

If you join this study, you should understand that you will not own your data, and should researchers use them to create a new product or idea, you will not benefit financially.

15. What does your signature on this consent form mean?

Your signature on this form means that: You understand the information given to you in this form, you accept the provisions in the form and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

_____

Signature of Participant (Print Name) Date/Time

_____

Signature of Person Obtaining Consent (Print Name) Date/Time

_____

Signature of Witness to Consent Procedures (Print Name) Date/Time

(optional unless IRB or Sponsor required)

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

APPENDIX G

JOHNS HOPKINS SCHOOL of MEDICINE eIRB2

Date: Friday, April 20, 2018 4:47:19 PM
View: AP: General Info

Print Close

Application
NA_00087648
Yuri Agrawal

1 - General Information

ID: NA_00087648

1. * **Principal Investigator:**
*Click **Select** to choose PI:*
Yuri Agrawal

2. * **Will the PI obtain consent for this study ?**
● **Yes** ○ No

3. * **Is the PI a JHHS RN?**
○ Yes ● **No**

4. * **Indicate the PI's primary affiliation:**
(Select "Other (Affiliation Not Listed)" if the PI's primary affiliation is not listed):
Otolaryngology - Broadway

5. * **Title of Study:**
Longitudinal Tracking of Balance and Falls

6. * **Provide a BRIEF statement of your research question and plan:**
The goal of this project is to explore factors related to imbalance and falls in patients, with a particular focus on vestibular loss. In understanding what factors increase fall risk, methods of prevention in vestibular therapy can be improved to reduce these risks. We will evaluate several potential fall risk factors, and track the falls of patients over time through monthly fall calendars, weekly text messages, and/or quarterly phone calls.

7. * **Select the type of review requested:**
Expedited

8. * **Will an external IRB act as the IRB of record for this study?**
○ Yes ● **No**

9. **What kind of study is this?**
Single-site study

11. * **Does this project ONLY involve retrospective review of records already in existence at the time of this IRB application submission?**
○ Yes ● **No**

12. * **Is this a quality improvement project?**

○ Yes ● **No**

13. * **Is this a resubmission of an expired, terminated, withdrawn or disapproved application?**
○ Yes ● **No**

15. * **Is this a conversion of an active study already approved by a Hopkins/Affiliates IRB (including the JHM All Children's Hospital IRB)?**
○ Yes ● **No**

19. * **Estimated time to complete this study:**
5 years

20. **Study Team Members:**

*Click **Add** to add new Study Team members. Click **Update** to modify existing Study Team member information.*

	Last	First	Degrees	JHED Dept	Primary Affiliation	Role	Consenting Hopkins participants	Receive Notifications	Agree To Participate
View	Carey	John	M.D.	SOM Oto Otology	Otolaryngology - Broadway	Co-Investigator	yes	yes	yes
View	Cullen	Kathleen	PhD	SOM BME Systems Neuroscience	Biomedical Engineering	Co-Investigator	yes	yes	yes
View	Gandhi	Priyal	n/a	Medicine (M.D. Program)	Otolaryngology - Broadway	Co-Investigator	yes	yes	yes
View	Kamil	Rebecca	MD	Otolaryngology-Head and Neck Surgery	Otolaryngology - Broadway	Co-Investigator	yes	yes	yes
View	Kheradmand	Amir	MD	SOM Neuro Vestibular Neurology	Neurology - Broadway	Co-Investigator	yes	yes	yes
View	Makhina	Maria		SOM Admin FJHM Oto Head and Neck Surgery	Otolaryngology - Broadway	Co-Investigator	yes	yes	yes
View	Ostrander	Benjamin	n/a	Bioengineering Innovation	Otolaryngology - Broadway	Co-Investigator	yes	no	yes
View	Pearson	Deryck	n/a	SOM Oto Otolaryngology Research	Otolaryngology - Broadway	Co-Investigator	yes	yes	yes

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[redacted]

EDUCATION

Towson University
Towson, Maryland
- Doctor of Audiology (Au.D.), anticipated May 2019

Brooklyn College, The City University of New York
Brooklyn, New York
- Bachelor of Art, Speech-Language Pathology/Audiology, September 2014

Yaroslavl State Pedagogical University
Yaroslavl, Russia
- Bachelor of Art, Teacher of History and English as Second Language, July 2009

CLINICAL EXPERIENCE

Audiology Intern, ENTAA Care
Columbia, Maryland January 2018-May 2018
- Performed comprehensive audiological evaluation for adults and children
- Perform adult and pediatric hearing aid evaluation, fitting, and repairs from a range of manufacturers
- Performed videonystagmography (VNG) testing and rehabilitation for Benign Paroxysmal Positional Vertigo (BPPV)
- Performed electrophysiological evaluations including OAE, ABR, and ECochG

Audiology Intern, The Hearing and Speech Agency (HASA)
Baltimore, Maryland May 2017- July 2017, December 2017-January 2018
- Perform comprehensive audiological evaluation for adults and children
- Perform adult and pediatric hearing aid evaluation, fitting, and repairs from a range of manufacturers
- Perform comprehensive auditory processing disorder testing
- Provide interpretation services for Russian-speaking patients

Audiology Intern, Chesapeake Ear Nose & Throat
Owings Mill, Maryland August 2017-December 2017
- Performed comprehensive audiological evaluation for adults and children
- Performed adult and pediatric hearing aid evaluation, fitting, and repairs from a range of manufacturers
- Performed videonystagmography (VNG) testing and rehabilitation for Benign Paroxysmal Positional Vertigo (BPPV)
- Provided interpretation services for Russian-speaking patients

Audiology Intern, Chesapeake Hearing Centers
Annapolis, Maryland March 2017 – May 2017

- Performed comprehensive audiological evaluation for adults and children
- Performed adult and pediatric hearing aid evaluation, fitting, and repairs from a range of manufacturers
- Assisted with videonystagmography (VNG) testing

Audiology Intern, Johns Hopkins Bayview Medical Center
Baltimore, Maryland January 2017- March 2017

- Performed comprehensive audiological evaluation for adults and children
- Performed adult and pediatric hearing aid evaluation, fitting, and repairs from a range of manufacturers

Audiology Intern, Towson University Hearing and Balance Center
Towson, Maryland January 2016 – December 2016

- Performed comprehensive audiological evaluation for adults and children
- Performed adult and pediatric hearing aid evaluation, fitting, and repairs from a range of manufacturers
- Performed comprehensive auditory processing disorder testing

RESEARCH EXPERIENCE

Doctoral Thesis – anticipated defense in May 2018
Vestibular Dysfunction and Brain Fog
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FELLOWSHIPS AND AWARDS

- Better Hearing Centers Fellowship, Towson University

PROFESSIONAL ORGANIZATIONS

- Member at Student Academy of Audiology (SAA), 2015 – Present
- SAA Treasurer, July 2016 – July 2017
- Member at Sigma Alpha Eta (SAE), the Speech and Hearing Society of Brooklyn College, September 2012 – August 2014