Decoding Neurophysiological and Gaze-Pattern Changes in Response to Vestibular Schwannoma

Background: The vestibular system, located in the inner ear, provides sensory information regarding spatial positioning and balance, enabling coordination of movement and orientation[1]. Additionally, the vestibular system plays a key role in enacting compensatory eye movements in response to body movement through the vestibulo-ocular reflex (VOR)[1]. This system can become unilaterally impaired in the presence of vestibular schwannoma, a benign tumor that develops on the vestibulocochlear nerve connecting the sensory organs to the brain[2]. Due to the vestibular system's active role in locomotion, impairment via vestibular schwannoma may lead to balance deficiency, vertigo, and oculomotor process changes[2]. Previous work has demonstrated that in patients with vestibular schwannoma, head movements during locomotion and gaze stability exercises are less rapid and the VOR is impaired[2,3]. Encouragingly, resection, or removal, of vestibular schwannoma has been demonstrated to result in improvement of kinematic parameters and other head movements, with major changes occurring within the first six weeks post-operation[4]. Generally, normal vestibular activity is reflected in the parieto-insular and temporo-parietal junctions; however, little is known about cortical changes that occur due to vestibular impairment, with most studies focusing on kinematic parameters and quantification of specific visual reflexes[5]. Therefore, there is **a need to examine the impact of vestibular schwannoma on neural activity at large.** Obtaining this information about the ways the human brain copes with vestibular system deficiency will elucidate both patterns of neural plasticity in response to specific sensory input alteration, and how best to approach treatment of those who are impacted by vestibular schwannoma. ***I propose to determine the patterns of neural activity and gaze focus in response to locomotor tasks in people with vestibular schwannoma, both pre- and post-resection.*** This work will be conducted across three Aims: first, a comparison of electroencephalography (EEG) and gaze-tracking patterns in healthy subjects and vestibular schwannoma patients; second, a longitudinal study of EEG and gaze patterns in vestibular schwannoma patients pre- and post-resection; finally, generation of a support vector machine (SVM), a machine-learning technique which will discriminate between gaze patterns of patients with vestibular schwannoma and healthy controls.

Intellectual Merit: This project will contribute to the body of knowledge surrounding normal vestibular function, as well as provide insight into the specific pathological state inherent to vestibular schwannoma. The insight into the changes in gaze functionality will be especially important because the impact of vestibular schwannoma on overall gaze patterns is not well-understood beyond interruption to the VOR. Changes to further parameters such as saccade frequency, fixation time, and primary areas of focus during locomotion are unknown. This project will elucidate changes in those patterns.

Research Plan:

Aim 1: Collection of baseline patterns in vestibular schwannoma patients vs. healthy subjects

Hypothesis: Vestibular schwannoma patients will display greater primary motor cortex activation than healthy control subjects during gait, representing a more effortful process due to balance impairment.

In this phase, we will focus on establishing a baseline of functionality in healthy subjects and patients with vestibular schwannoma, recruited from Johns Hopkins Acoustic Neuroma Center, a specialty clinic focused on the treatment of vestibular schwannoma. Testing will consist of a modified functional gait assessment (FGA) battery. The 'gait with eyes closed' portion of the FGA will be excluded, due to the inability to record gaze location while eyes are closed. During the FGA, subjects will have gross brain activity recorded via a 58-channel EEG cap connected to a wearable Arduino Uno microcontroller to allow for continuous mobile data collection. Additionally, subjects will don wearable eye-tracking glasses to assess continuous gaze location. This phase will conclude with successful collection of gaze-tracking and EEG data for a matched number of healthy subjects and vestibular schwannoma patients executing the FGA tasks.

Aim 2: Longitudinal study of vestibular schwannoma resection

Hypothesis: Between six weeks and six months after vestibular schwannoma resection, patterns of neural activity in vestibular schwannoma patients will become more like that of healthy subjects during gait.

This phase will enact a longitudinal study of patients with vestibular schwannoma pre-resection, approximately six weeks post-resection, and at least six months post-resection. This experimentation will consist of the same paradigm as Aim 1, with subjects performing the modified FGA. Additionally, during this phase, the EEG signal collected in Aim 1 and Aim 2 will be processed and analyzed. Preprocessing

will consist of an independent component analysis, wherein the multivariate EEG signal for each subject will be decomposed into additive 'components', which combine at different weights to compose the overall EEG signal. These components will be assessed via visual inspection to remove extraneous signal, such as eye blinks and motion artifacts. Then, processed data will be examined for event-related potentials at several key points in the gait cycle. This phase will conclude with the accomplishment of two tasks: successful collection of gaze-tracking and EEG data for vestibular schwannoma patients pre- and post-resection, and analysis of differences in patterns of neural activation between healthy controls, pre-resection vestibular schwannoma patients, and post-resection vestibular schwannoma patients.

Aim 3: Generation of Support Vector Machine to categorize gaze patterns

Hypothesis: Individuals with vestibular schwannoma will display distinct gaze patterns, including greater gaze latency to area of interest, as compared to healthy control subjects.

This phase will center around the generation and validation of a support vector machine (SVM) that will enable automatic machine classification of vestibular schwannoma patients versus healthy controls. An SVM is a supervised machine learning approach that uses a hyperplane to split groups of variables, or support vectors, into discrete classes (shown in two dimensions in **Figure 1**); once trained on the stereotypical values for each class, it compares new data to those clusters to classify the state of the new input[6]. An SVM has been used to accurately detect pathology based on gaze patterns; specifically, individuals with dyslexia versus healthy controls while reading text[6]. Measured parameters will include number of saccades, number of gaze fixations in key areas of interest (ground underfoot, ground ahead of stride, wall), length of gaze fixations, and latency of gaze arriving at areas of interest. Within this model, some erroneous classification is inevitable. Because the primary purpose of the model is quantifying impacts of vestibular schwannoma to the ocular system, it is preferable to bias the model towards detecting vestibular schwannoma in order to find any and all gaze-pattern disruptions. Accordingly, the SVM will be tuned to have higher sensitivity to prevent false negatives. This phase will conclude with the demonstration that the resultant SVM is able to discriminate between the gaze patterns of healthy individuals and those who suffer from vestibular schwannoma, with at least an 85% detection rate for positive cases.

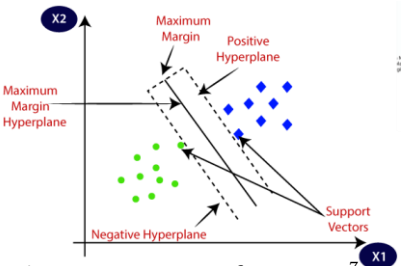

***Figure 1**: Design of an SVM* [7]

Alternative Approaches: An SVM can have limited efficacy if the training dataset is of insufficient size. If there is not be a significant dataset that will allow for training of the model and model accuracy is below the 85% threshold, an alternative approach may be the use of a convolutional neural network (CNN), which consists of a cluster of signal-transmitting kernels that loosely resemble neurons. A CNN has previously been used to classify gaze-tracking data based on what website a user was viewing; however, this methodology has not been extended to pathology detection[8]. If needed, this possibility could be explored.

Facilities: This work will be conducted with Dr. Kathleen Cullen at the Cullen Laboratory at Johns Hopkins University. This laboratory has previously conducted studies of vestibular schwannoma patients using kinematic parameters and is equipped to continue this work with other methodologies.

Broader Impact: While the primary purpose of this work is to learn about the unimpaired vestibular system through a study of vestibular schwannoma as a disease state there is potential for secondary application as a diagnostic measure. The diagnostic process for vestibular schwannoma is two-stage – first-round testing consists of a battery of hearing tests, and if those tests suggest the presence of a tumor, second-round testing consists of an MRI with contrast. With the rising costs of healthcare in the United States, finances can be a prohibiting factor to patients pursuing this diagnostic testing. The creation of a lower-cost intermediate diagnostic would prevent unnecessary clinic visits for final diagnostic testing for patients whose hearing loss may have a different cause. If the SVM can recognize patients with vestibular schwannoma, then an intermediate gaze-tracking diagnostic tool could be developed and used to screen patients with hearing loss to determine whether vestibular schwannoma is a likely culprit for their symptoms.

References: **1.** K. Cullen, *Nat Rev Neurosci,* 2019; **2.** A. Batuecas-Caletrio et al. *Laryngoscope,* 2015; **3.** L. Wang et al. *Sci Rep*, 2021; **4.** O. Zobeiri et al. *Sci Rep*, 2020; **5.** E. Nakul et al. *Front Neurol*, 2021; **6.** L. Rello et al. *W4A '15,* 2015; **7. "**Support Vector Machine", *javaTpoint*; **8.** Y. Yin et al. *ICMLA '18*, 2018.