The Effects of

Cervical Nerve Stimulation (CNS)

on Fall Risk

by

Itai Kreisler

A Thesis Presented in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Approved April 2019 by the
Graduate Supervisory Committee:

Thurmon Lockhart, Co-Chair
William "Jamie" Tyler, Co-Chair
Sarah Wyckoff

ARIZONA STATE UNIVERSITY

May 2019

ABSTRACT

Every year, 3 million older people are treated for fall injuries, and nearly 800,000 are hospitalized, many of which due to head injuries or hip fractures. In 2015 alone, Medicare and Medicaid paid nearly 75% of the $50 Billion in medical costs generated by falls. As the US population continues to age, more adults are beginning to deal with movement related disorders, and the need to be able to detect and mitigate these risks is becoming more necessary. Classical metrics of fall risk can capture static stability, but recent advancements have yielded new metrics to analyze balance and stability during movement, such as the Maximum Lyapunov Exponent (MLE). Much work has been devoted to characterizing gait, but little has explored novel way to reduce fall risk with interventional therapy. Targeting certain cranial nerves using electrical stimulation has shown potential for treatment of movement disorders such as Parkinson's Disease (PD) in certain animal models. For human models, based on ease of access, connection to afferents leading to the lower lumber region and key brain regions, as well as general parasympathetic response, targeting the cervical nerves may have a more significant effect on balance and posture. This project explored the effects of transcutaneous Cervical Nerve Stimulation (CNS) on posture stability and gait with the practical application of ultimately applying this treatment to fall risk populations. Data was collected on each of the 31 healthy adults (22.3 ± 6.3 yrs) both pre and post stimulation for metrics representative of fall risk such as postural stability both eyes open and closed, Timed-Up-and-Go (TUG) time, gait velocity, and MLE. Significant differences manifested in the postural stability sub-metric of sway area with subject eyes open in the active stimulation group. The

additional 8 metrics and sub-metrics did not show statistically significant differences among the active or sham groups. It is reasonable to conclude that transcutaneous CNS does not significantly affect fall risk metrics in healthy adults. This can potentially be attributed to either the stimulation method chosen, internal brain control mechanisms of posture and balance, analysis methods, and the Yerkes-Dodson law of optimal arousal. However, no adverse events were reported in the active group and thus is a safe therapy option for future experimentation.

ACKNOWLEDGMENTS

I'd like to thank my thesis committee, Dr William "Jamie" Tyler, Dr Thurmon Lockhart, and Dr Sarah Wyckoff for all their support and insight during my research. I'd also like to thank the members of the Locomotion and Tyler Labs for their assistance in data collection and analysis of for this project, but also years past which have led me to this point. Most importantly, my parents and family have played an immense role in instilling the drive to keep learning and discovering as I grow, and to them I am eternally grateful.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF EQUATIONS

Page

OVERVIEW

This project seeks to determine the effectiveness of Cervical Nerve Stimulation (CNS) as an interventional technique to increase stability and decrease fall risk. Classical analysis of stability has been performed through static gait parameters such as center of pressure and center of mass, but not much work has explored understanding stability during movement. Since most falls occur during movement, metrics like the Maximum Lyapunov Exponent (MLE) can allow for a better understanding of how to quantify changes in active gait. By harnessing these metrics, the effects of different treatments or conditions that can either improve or worsen an individual's balance can be evaluated. One promising technique, Transcutaneous Electrical Nerve Stimulation (TENS), when targeting cranial nerves such as the vagus and trigeminal nerves, has been shown to have a promising future in treating neuropathological movement diseases such as epilepsy, and can be easily accessed noninvasively through external cutaneous electrodes (Soss et al.). The C3-C5 cervical region of the spine is ideal for stimulation as it is both easily accessible and has connections to the nerves in the lumbar region of the spine associated with gait and balance and may influence the autonomous pathways within the brain. Additionally, since this external stimulation can have a major effect on neural activity and neural pathways, there exists investigative potential for this parasympathetic response to increase balance. By utilizing non-invasive data collection and analysis methods paired with new treatments, better rehabilitation pathways can be identified to decrease fall risk in the most fall prone populations.

BACKGROUND

Older Adult Falls

As the population continues to age, people 65 years and older have been experiencing life threatening falls at an increased frequency and at a lower reporting rate of less than 50% (Stevens et al.). Broken bones, head injuries, and other severe injuries occur in roughly 20% of falls (Alexander et al.). Due to the nature of a fall injury, risk doubles for a second fall once the first fall occurs (O'Loughlin et al.). In 2015 alone, nearly 95% of the 300,000 older adults hospitalized for injuries were caused by hip fractures and generated over $50 Billion in healthcare costs(Florence Curtis S. et al.). Medicare and Medicaid covered nearly 75% of these costs (*Important Facts about Falls | Home and Recreational Safety | CDC Injury Center*). In addition to the added strain on the healthcare system, many elderly individuals also take medications which increase risk factors for falling injury such as anticoagulants which increases the severity of brain injury, as well as the mortality rates of preinjury users (*The Impact of Preinjury Anticoagulants and Prescription Antiplatelet Agents on Outcomes in Older Patients with Traumatic Brain Injury | Ovid*). A common result of falls in older adults is a decreased daily activity, which is critical importance to maintain strength and preventing future falls and injury (Vellas et al.). The CDC identified a number of other risk factors, including certain medications like anti-depressants, tranquilizers, and sedatives, environmental factors like obstacles, slippery or uneven surfaces, and internal factors lower body weakness, vitamin D deficiency, and gait and stability difficulties, which have also been shown to lead to an increase in falls (*Important Facts about Falls | Home and Recreational Safety |*

CDC Injury Center). Certain measures can be taken to influence these factors such as balance training, strength training, vision correction, reducing environmental hazards, and medication adjustment, but often do not simply because of a lack of awareness of their fall risk. While these factors can be directly mitigated, people can also consciously adjust certain factors to minimize fall risk such as gait speed, which has been shown to have an impact on overall stability (England and Granata). Understanding how these factors play into overall fall risk is becoming increasingly important to not only identify at risk patients but also develop and test new interventional methods (Kreisler et al.).

Posture Stability and Gait Velocity

Both postural stability and certain metrics within gait velocity have been correlated with fall risk and have been used classically to understand overall stability (Melzer et al.), (Maki). Generally, a reduction in gait speed is associated with increased dynamic stability (England and Granata). While a decreased gait velocity may lead to increased stability, the internal control mechanisms used by the brain will opt for an increased speed and lower dynamic stability to optimize metabolic costs and motor control in healthy people. Slower gait in characterized by increased quadricep activity, which is more metabolically expensive to use due to the size of this muscle and its associated groups. In one study, quantitative measure of gait characteristics, such as gait velocity and stride length, indicated structural brain abnormalities in high functioning adults, suggesting the connection between gait and the internal brain control mechanisms which may be affected by other pathologies (Rosano et al.). The changes in gait velocity are magnified by the effects of both conscious and subconscious fear of falling (England and Granata). Changes in posture stability is also used as a metric for fall risk, and have been suggested to be an important tool in identifying elderly fallers (Melzer et al.).

Functional Neuroanatomy of Posture and Gait Control

The internal brain control mechanisms of gait are theorized to break into two general categories, both of which may be influenced by CNS, as described in Takakusaki 2017. One such gait is considered normal and automatic, which involves postural reflexes, body segment placement, and optimal muscle tone primarily governed by nervous structures such as the mesopontine tegmentum located dorsal to the midbrain, and associated with motor control and arousal, as well as the spinal locomotor network descending from the brainstem (Tsang et al.). The second type of gait, characterized by cognitive processing due to an unfamiliar environment, is theorized to be controlled primarily in the temporoparietal association cortex, and heavily influenced by understanding of self-body and body schema. Since balance and adaptable posture and gait control are very complex systems, the brain uses multi-sensory inputs to somatosensory, visual, and vestibular information as well as these different regions of the brain to achieve equilibrium (Takakusaki).

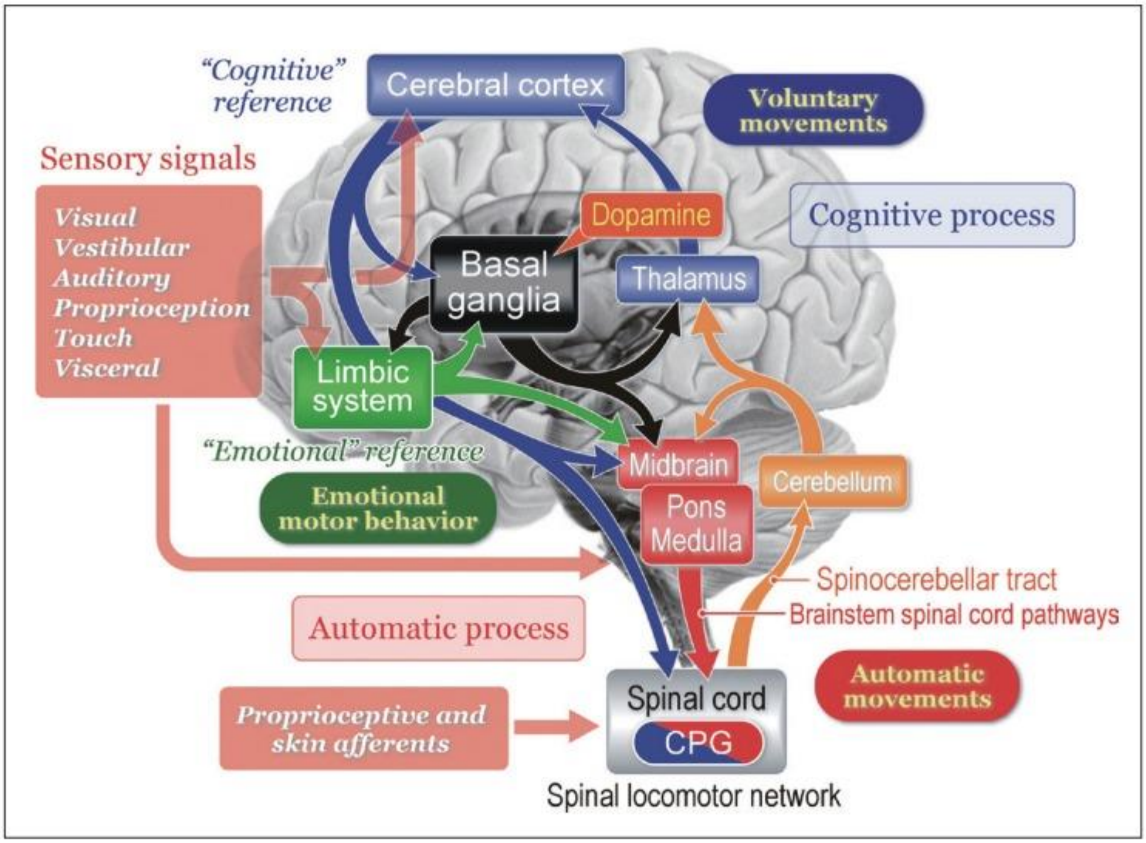

Figure 1. The Basic Signal Flow of Postural Control Indicating Multiple Sensory Inputs. Reproduced from Takakusaki 2017.

Other structures such as the basal ganglia, also associated with voluntary motor control, as well as the cerebellum, are known to influence balance and movement and play a large role in both types of gait (Lanciego et al.), (*Cerebellum (Section 3, Chapter 5) Neuroscience Online: An Electronic Textbook for the Neurosciences | Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston*). Other inputs such as emotional inputs to control motor function from the limbic system can elicit fight or flight type behavior. Regardless of the source of the motor control input, much of the processes to regulate gait are governed largely by subconscious activations of neurons in the brain stem and spinal cord. Within the spinal locomotor network, Central Pattern Generators (CPGs) create basic locomotion patterns without the subject's conscious effort. Perturbation of any one of these complex networks through electrical stimulation may have significant effects on the control mechanisms, especially through stimulation of nerves which project to and from these systems. The mesopontine tegmentum, identified as a key structure in gait control, contains nuclei of both the trigeminal and vestibulocochlear cranial nerves, which were targeted through CNS in this experiment (Winn).

Electrical Nerve Stimulation

The use of electricity for pain management dates back to the ancient Egyptians, who used certain fish to shock body parts to reduce pain, and came into the modern realm of science first in the 1800s, and more seriously in the 1960's with Melzack and Wall's Gait Control Theory of Pain (Walsh). The basic idea behind this theory was that the brain can only perceive a certain number of signals from peripheral nerves, so activation of major afferent nerve groups could essentially block the brain from feeling the pain felt by smaller nerves. This led to a boon in the interest in medical research understanding what could be affected by nerve stimulation, including stimulation of the cranial nerves to mitigate a host of different issues. Stimulation of different cranial nerves have been shown to elicit different physiological reactions based both on direct projections and generalized effects on the body. Electrical nerve stimulation of the vagus nerve was first observed to alter brain activity and terminate seizures roughly 30 years ago, and has since been utilized in a number of different applications and devices (ZABARA). The vagus nerve is the 10th cranial nerve, originating from four nuclei in the medulla oblongata, and has the most extensive distribution and course of all of the cranial nerves (Ogbonnaya and Kaliaperumal). These nuclei are associated with certain motor neurons, gastrointestinal, taste, respiratory, and somatic sensory neurons around the upper body. Although VNS is a relatively new treatment, it has been approved to treat both refractory epilepsy and chronic treatment resistant depression (Howland). While VNS has been used in a wide variety of applications such as bipolar and anxiety disorders, refractory headaches, and obesity, the FDA has not given approval for any of these uses (*The Emerging Use of Technology for the Treatment of Depression and Other Neuropsychiatric Disorders. - PubMed - NCBI*). While most devices are implantable, transcutaneous VNS has been shown to be comparable to both invasive and auricular VNS, affecting brain areas including as regions of the parabrachial area, primary sensory cortex, and the basal ganglia which is associated with motor function (Frangos and Komisaruk). Recently, VNS has been identified as a potential novel treatment for Parkinson's Disease (PD) in rat models based on increased locomotor activity in one study ("Vagus Nerve Stimulation as a Novel Treatment Strategy for Parkinson's Disease"). Trigeminal Nerve Stimulation (TNS) has shown promise in a few areas such as one open-trial pilot study where TNS significantly improved youth's ADHD-IV rating score (McGough et al.). In another study, symptoms of post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) were both significantly decreased in an 8-week outpatient trial (Cook et al.). While these trials lacked the appropriate study design rigor needed to confirm any serious effects, one randomized controlled and double blind study found that similar to VNS, TNS does show initial potential for acute treatment of drug resistant epilepsy (DeGiorgio et al.). In one long term study, more conclusive statistical differences were established where TNS treatment was not only tolerated but was correlated with a decrease in seizure episodes. Since the broad connections of cranial nerve stimulation are known to input to the nonandrogenic system, the parasympathetic response will create changes in arousal processing of sensory information (Berridge and Spencer). These changes have the potential to show a significant change in motor related areas of arousal which will cascade down to affect postural and dynamic stability. While VNS and TNS have proven promising for several pathologies, this project focused on stimulation of the cervical nerves and their afferents in the cervical region of the spine due to its accessibility, connection to lower spinal nerves, and potential for general parasympathetic response. The location of the electrodes is on the C3-C5 vertebrae, which shares many common connections with other spinal nerves in the lumbar and sacral regions affecting the lower extremities. Stimulation of cervical nerves, which have afferents running all along the spine, may also show changes in the autonomous brain control mechanisms of gait. The primary targets of CNS are the cervical plexus and trigeminocervical complex with projections in the vestibulocochlear and great auricular nerve. As mentioned previously, nuclei of both the vestibulocochlear and trigeminal nerve appear within the mesopontine tegmentum associated with gait control in the brain, indicating potential for significant effects on balance and ultimately fall risk.

An alternative stimulation pathway to increased balance is the generalized sympathetic suppression of TENS as seen in Tyler et al, 2015. Transdermal neuromodulation targeting the ophthalmic and maxillary divisions of the right trigeminal nerve and cervical spine nerve afferents were observed to show not only decreased basal sympathetic tone, but also significantly lower levels of tension and anxiety (Tyler et al.). Since these findings focused primarily on acute stress reduction, this pathway may prove more effective when modulating the consciously controlled walking in stressful situation such as PD patients. Since cognition has been shown to impact freezing of gait (FOG) in patients with PD, the affect of modulating these pathways will likely be significant (Maruyama and Yanagisawa). In this study, healthy individuals will be participating in tasks that will fall under the autonomous walking category and will likely be more affected by a more targeted stimulation of associated afferents and projections of nerves directly involved with motor control as described previously.

Fall Risk Analysis

An individual's dynamic stability can be the cause of reactance to perturbations, while the classic gait parameters can show very little, which is true in many elderly people. It is known that many elderly individuals change their gait by widening their stance and shortening their stride, which should increase stability, yet a much higher fall risk is seen with increased age, possibly due to the decrease in dynamic stability. By analyzing gait as a collection of individual strides and the bridges that connect them, it is much easier to paint a more complete picture and understand how to identify patients who are more fall prone prior to a severe accident (*Group Differences among Fall-Prone Individuals and Healthy Old and Younger Counterparts Utilizing Nonlinear Stability Measures - Journal of Biomechanics*). Collection methods have been improving and developing over the past few decades, moving from simple motion capture and a labor intensive mathematical analysis to smaller devices like inertial measurement units (IMUs) that can collect accelerometer and gyroscope data at specific locations over long periods of time and send this data to a larger data storage unit (Liu et al.). Both sets of data, the classical gait parameters and the IMU data, can be used to calculate a dynamic stability metric as its efficacy is being continually researched. Fall risk can also change depending on various settings of the individual as well as the surface the individual is walking on, meaning different individuals can have varying levels of fall risk in virtually the same environments (Liu et al.). This lends itself to create the need for dynamic stability as a parameter which con represent more than an acute measure of fall risk. By analyzing the motor control and postural stability system entropies, differentiation of fallers and non-fallers can become clearer, but only when combinations of these analyses are used [15]. When considering entropy analysis, it is extremely important to consider even the most minute details, with research being done even on sensor placement during real time data collection for parameters such as FOG which can produce stability (Rezvanian and Lockhart). One area of research which is lacking is the effects of the perturbations on dynamic stability and its subsequent correlation to fall risk. In one previous study, virtual reality training was used to assess slip-induced falls, which resulted in a reduced incidence of falls in the trained group (Parijat et al.). Although this experiment yielded powerful results, it required complex analysis and expensive, virtually immobile machinery. If the dynamic stability can be extracted from simple sensors to yield similar results, the actionable applications and potential for a much larger data pool increase exponentially.

Currently, the Lockhart Monitor app has been developed to accommodate the dynamic stability calculation from a simple walking test, which is an immensely powerful tool to perform these analyses in real time and with minimal effort. Several potential concerns arise when using the iPhone app such as differences in height and weight affecting the MLE, however by normalizing the dynamic stability range to the length of the leg by incorporating the Froude Number, this can be avoided. The Froude Number is a dimensionless number defined as the ratio of the flow inertia to the external field, which in this case is simply the effect of gravity (*Froude Number*). The Lockhart Monitor allows for a quick measure of MLE after a simple walking test with minimal invasiveness. With this increased efficiency in data collection, the MLE has been analyzed more acutely, as it is currently hypothesized that the MLE can depend on internal brain control systems which are affected by perturbations such as the degree of conscious control a person has on his or her walking velocity (Takakusaki). For this study, it is hypothesized that Cervical Nerve Stimulation will produce a significant difference in stability and fall risk in patients after the treatment characterized by changes in postural stability, TUG time, gait velocity, and MLE.

MATERIALS AND METHODS

Data Collection

Data was gathered from 31 healthy young college-aged adults, ages 18 – 50 (22.4±6.3yrs) using the Lockhart Monitor App on the iPhone. After prescreening and blocking for neurological disorders and collecting pertinent parameters such as height and weight, subjects had the iPhone connected over their clothing to their lower back area on the L4-L5 spinal segment using an adjustable belt and iPhone clip. Once this was attached, the subject performed 5 tasks commonly used to assess balance and gait: 1) A 60 second posture stability analysis using center of pressure (CoP) with eyes open, 2) the same task with eyes closed, 3) a Timed-Up-and-Go (TUG) test, 4) a gait velocity test, and 5) an MLE test.

After the monitor was set up, the subject was asked to assume a normal standing position, with feet shoulder-width apart and hands at their sides, pick a spot on the wall to focus on, and to stay as still as possible. The start button was pressed, and the monitor beeped once to indicate data collection began. After 60 seconds, the monitor beeped again to indicate the data was captured. Parameters of sway area, sway path length, and sway velocity were recorded, and the raw accelerometer data was saved in the form of a .csv excel file and stored on the phone itself. The same test was repeated with eyes closed. Next, the TUG test was performed, measuring the time from a seated position to get up, walk a 3-meter distance, turn around, come back, and return to the seated position using the stopwatch of the iPhone. The gait velocity test involved reattaching the phone to the lower spine region, starting the test which would beep once to indicate baseline data collection, a second beep to indicate to the subject to start walking, and a third beep to indicate data was successfully collected once the subject crossed the pre-measured 15-meter mark line and stopped. For the MLE test, a similar setup to the gait velocity test was run, although the subject would continue walking until the phone had collected roughly 50 gait cycles necessary for the calculation, then beeped to indicate to the subject to stop, and beeped again to signal a successful metric calculation. All raw data gathered in trials using the iPhone Lockhart Monitor App was de-identified and stored locally on the iPhone in case of future use.

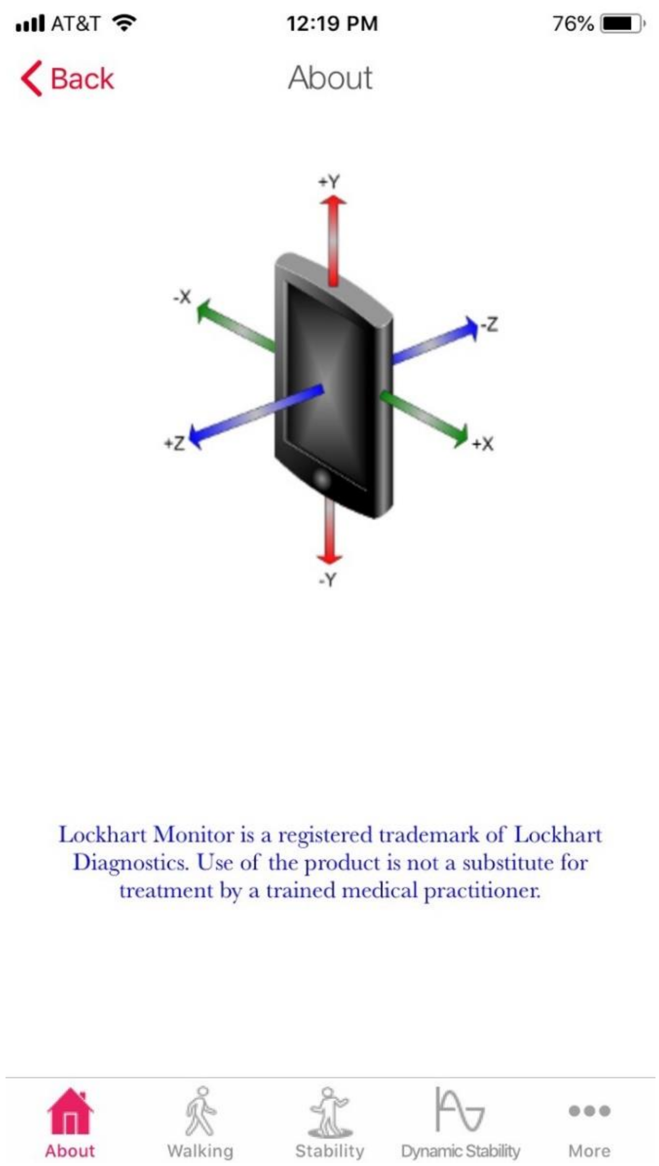

Figure 2. Screenshot of the Lockhart App Explaining Phone Axis Orientations. The X Plane Represents Medio-Lateral Movement, the Y Plane Represents Vertical Movement, and the Z Plane Represents Anterior-Posterior Movement.

Once the initial parameters were gathered, the TENS stimulation was administered to the subject. An active and sham group was used. After alcohol swabbing to remove the capacitive skin layer on the neck, two 2-inch PALS sticky electrodes were placed at the C3-C5 cervical region across the spine roughly .5 to 1 inch apart from the inner edges of the electrodes.

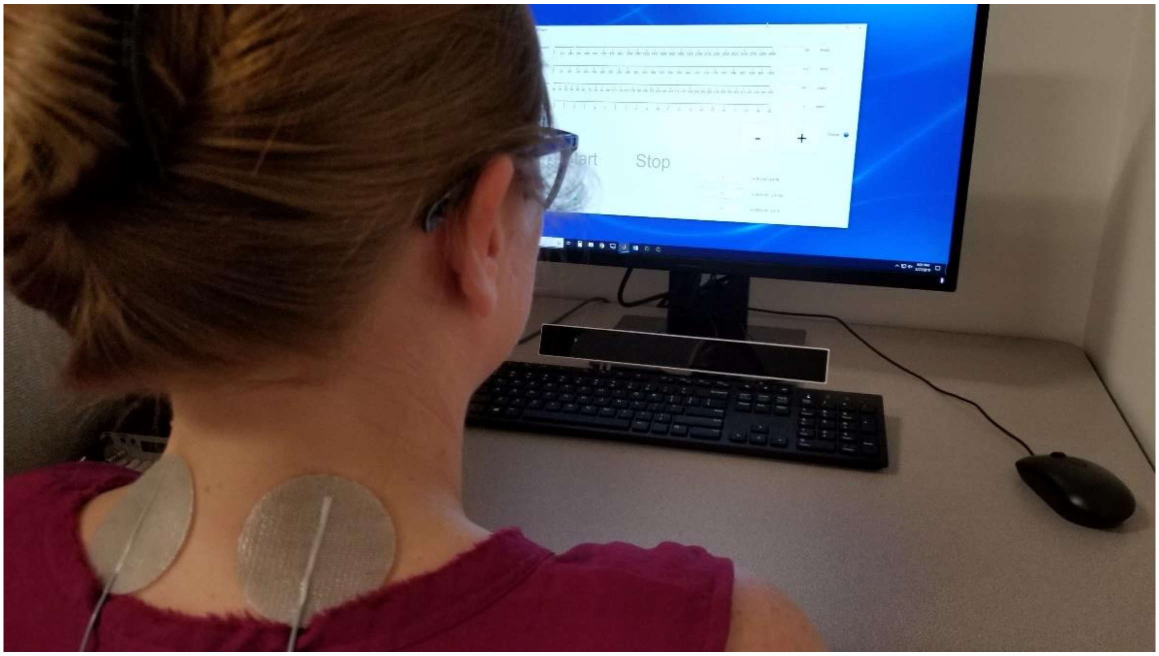

Figure 3. The Electrodes Placed on the Cervical Region of the Neck with the MATLAB Controller Visible on the Screen.

The test was run using a MATLAB controller previously developed by the lab, and a custom current controlled neurostimulator, or Remi V2.00, at a fixed 300Hz, pulse width of 350us, and a gap of 350us. The signal intensity was modulated by the subject from 0 to 20mA of current in .25mA increments and ranged between 4mA and 20mA for the active group (12.47±5.28 mA). During the 10 minutes of stimulation, the subjects were exposed to neutral visual stimuli to prevent excessive boredom. Once the stimulation was completed, the pads were removed, and the 5 balance and gait tasks were repeated, and appropriate data was recorded. Acute post-treatment and 24 hour follow-up surveys were collected to collect safety data and adverse events.

DATA ANALYSIS

Calculating the MLE

Calculating the Maximal Lyapunov Exponent involves a number of complex steps as described by Lockhart and Liu in *Differentiating fall-prone and healthy adults using local dynamic stability* (Lockhart and Liu) which are summarized in this section, based off previous work (Kreisler et al.). Stability is defined as a neuromuscular system's ability of dynamic walking equilibrium maintenance when affected by kinematic and control variability (Leipholz). Kinematic movements and disturbances to this system, when analyzed through engineering methods and different quantifications, can elucidate underlying patterns within the system. By understanding the system response, certain characteristics can be mathematically described, such as the rate at which these variabilities approach a steady state movement trajectory.

The Maximal Lyapunov Exponent is one such measure that is derived through non-linear dynamics. According to Takens' theorem, a chaotic dynamical system can be reconstructed from a series of observations of the state of the given system, based on conditions given by a delay embedding theorem, also known as a time delayed coordinate approach ("Takens's Theorem"). This means system invariants such as stability characteristics in human motor control can be described by the multi-dimensional state space reconstruction of the system. For this approach, the minimum embedding dimension (d_E) and time delay (T) must be determined, which is possible through the auto mutual information approach (*Practical Method for Determining the Minimum Embedding Dimension of a Scalar Time Series - ScienceDirect*) and the nearest false neighbors approach (Abarbanel et al.). An initial single dimension time series $x(t)$ can be reconstructed in the state space as $X(t)$, described below:

$$X(t) = [x(t), x(t+T), x(t+2T), \dots, x(t+d_E-1)T)]$$

Equation 1.

When reconstructing in the state space, dynamic stability, derived as the resistance of the motor control system to perturbations, can be assessed as the average divergence of neighboring trajectories. To determine the nearest neighbor, two points from separate strides which are closest together in the reconstructed state space are chosen, and this process is repeated for all data points. The Lyapunov exponent is obtained from this reconstruction. Dependent changes in kinematics variability are tracked through time by recording the distances between these points, resulting in a function of divergence over time which will diverge at a rate defined as the MLE:

$$\lambda(i) = \langle \ln[D_j(i)] \rangle \, / \, \Delta t$$

Equation 2.

here $D_j(i)$ represents the Euclidean distance between the jth pair of nearest neighbors after i time steps, Δt is the time series sample period, where $\langle \ln[D_j(i)] \rangle$ is the average of the values over all vaues of j.

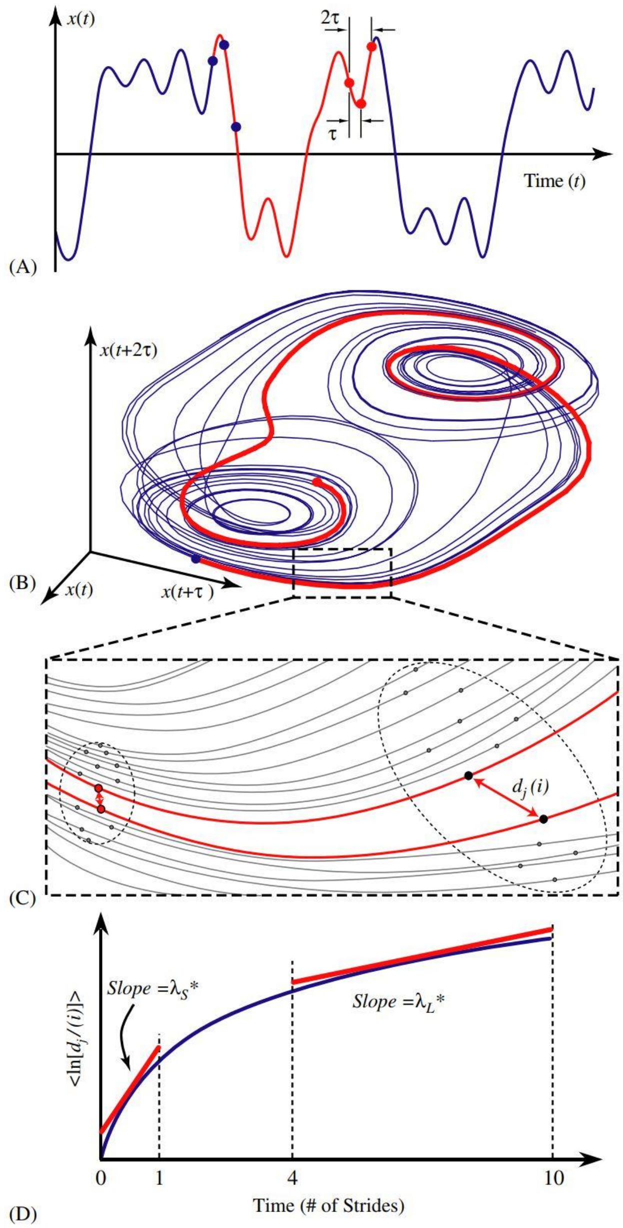

Figure 4. Schematic Mle Analysis. (A) Raw Time Series Data x(t) (B) Reconstruction in 3d State-space (C) Expanded Local View of State-space Showing Nearest Neighbors (D) Average Logarithmic Divergence $\langle ln[D_j(i)]\rangle$ of All Pairs of Neighboring Trajectories Vs Time, With MLE As Slope λ_s.

For this experiment, the MLE was described as a linear fit to the logarithmic divergence over time. This is chosen because perturbations will cause the divergence to grow exponentially over time, indicating that a higher MLE translates to a faster growing divergence and lower resistance to perturbation (Abarbanel). Ultimately, a higher MLE indicates a lower dynamic stability. Figure 4 represents this process graphically (Dingwell and Marin).

Statistical Analysis

The parameters collected in the methods section include postural stability with center of pressure metrics of sway area, sway path length, and sway velocity for eyes open and eyes closed, TUG time, gait velocity, and MLE. These metrics were collected both pre and post stimulation in the active and sham groups. A paired, two tailed T-test was performed on the two data sets for each parameter, with an alpha value of .05 selected for significance.

RESULTS

The sham group yielded no statistically significant different values. In the active group, the postural stability sub-metric of sway area during the eyes open test was statically significantly different at a p-value of .023, which was the only test to show a difference between the pre and post stimulation. The figures below summarize the average metrics of each task, both active and sham group, pre and post stimulation. No adverse events were reported on follow-up safety reports from the active group.

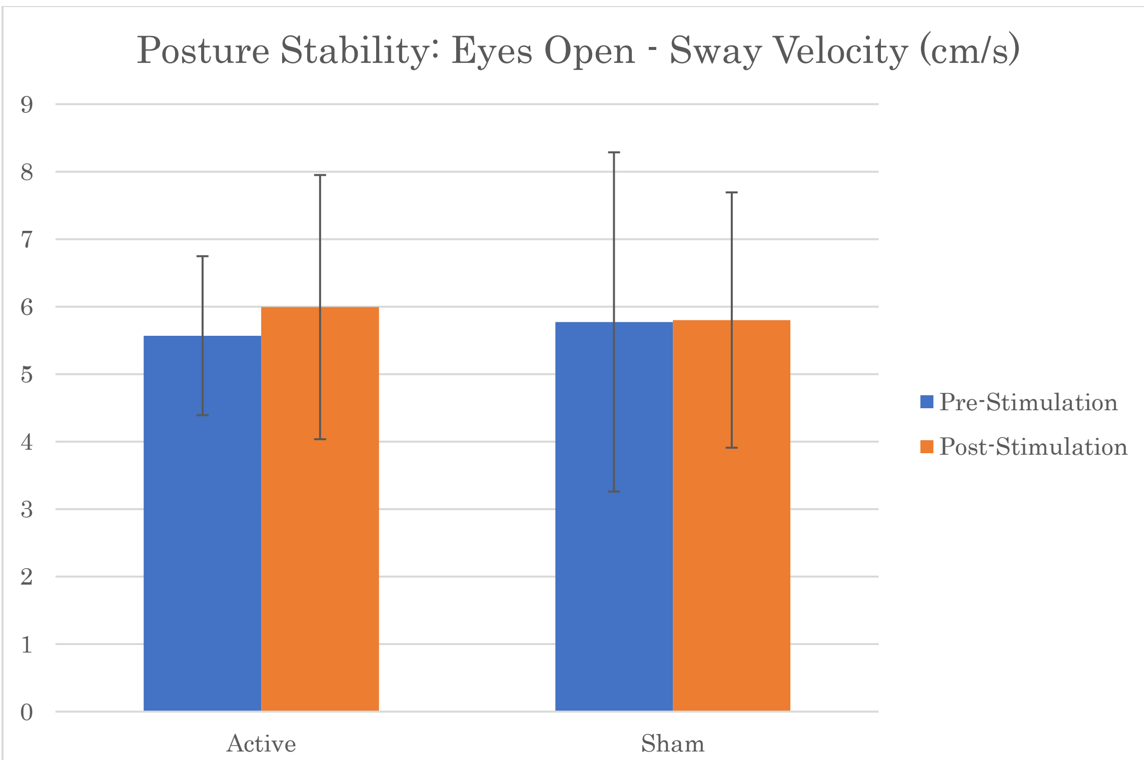

Figure 5. Average Values of Sway Velocity in the Eyes Open Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. No Significant Differences Were Observed.

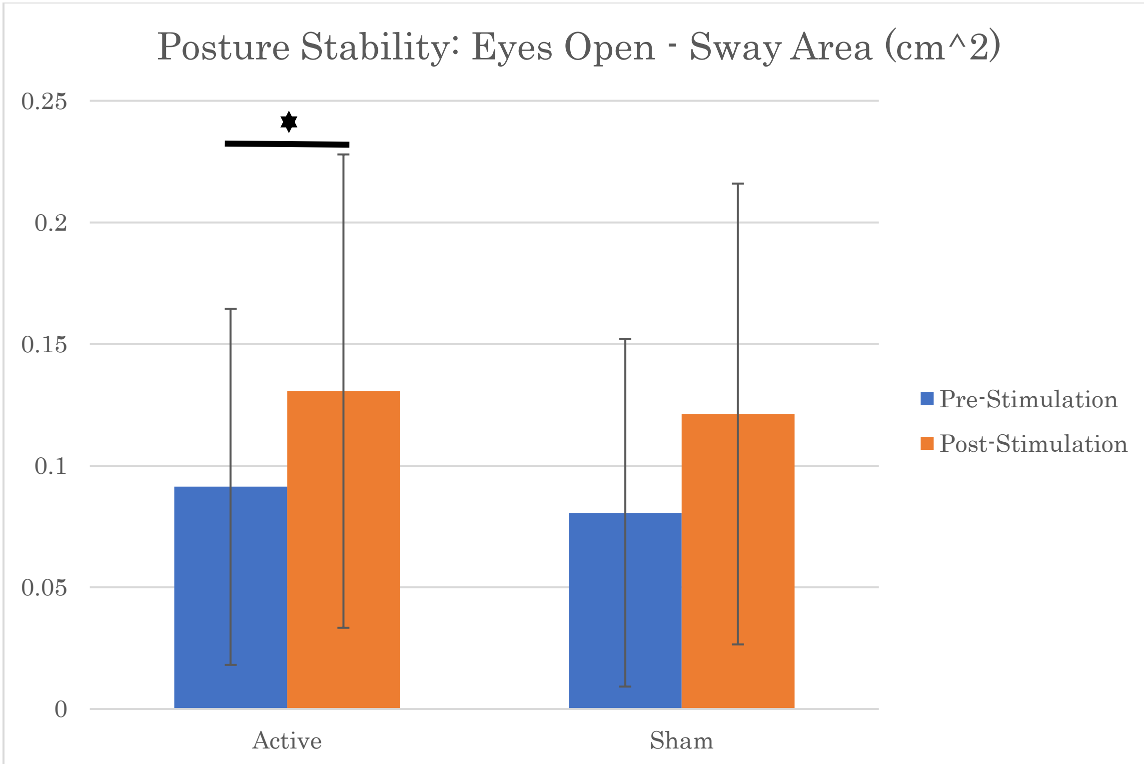

Figure 6. Average Values of Sway Area in the Eyes Open Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. Significant Differences Were Observed Between the Pre and Post Stimulation in the Active Group with a P-value Of .023.

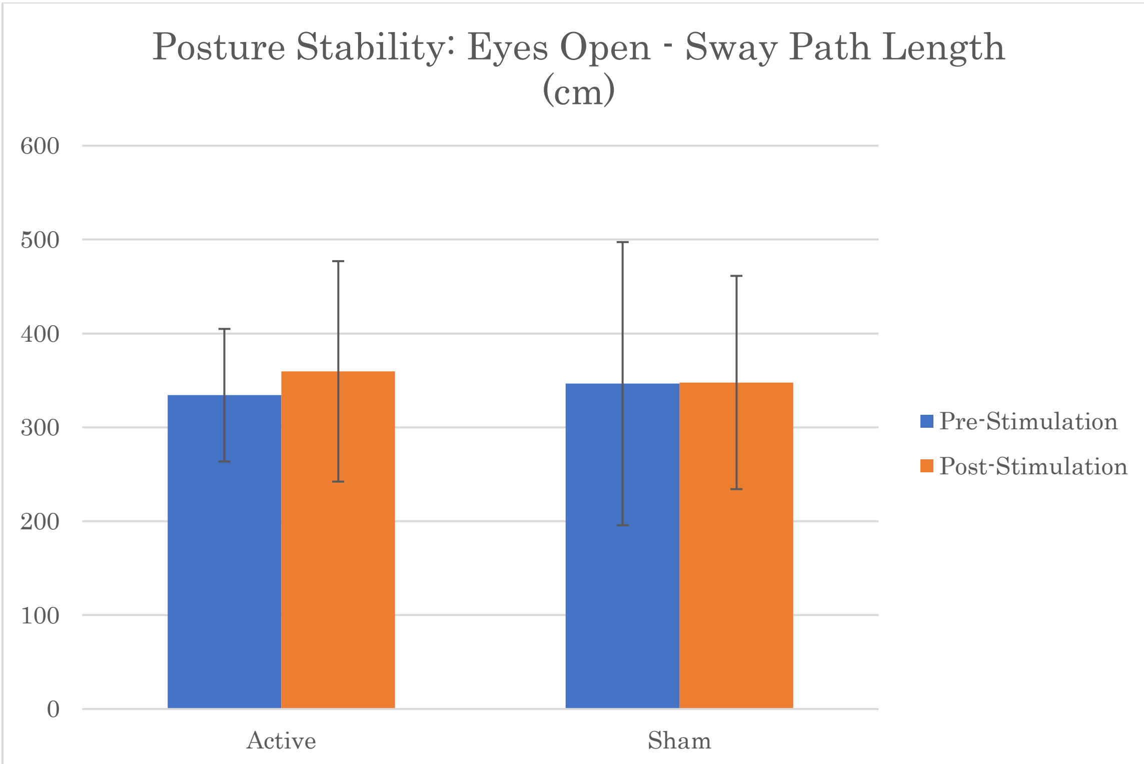

Figure 7. Average Values of Sway Path Length in the Eyes Open Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. No Significant Differences Were Observed.

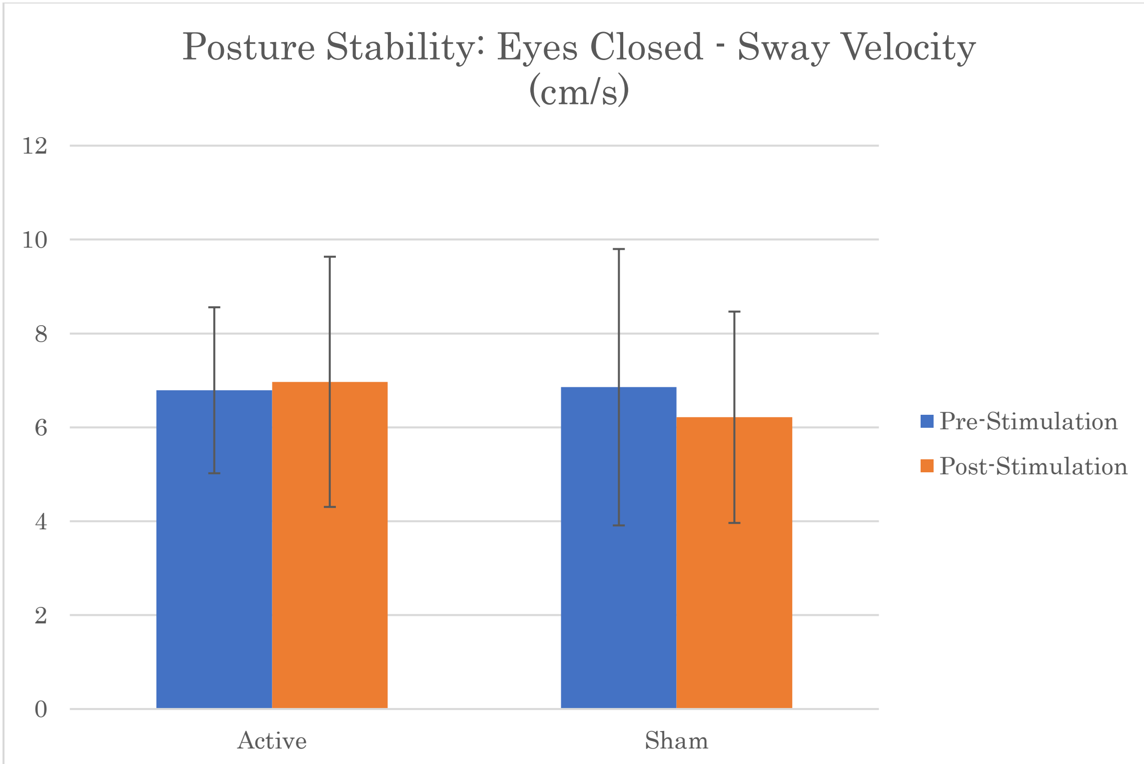

Figure 8. Average Values of Sway Velocity in the Eyes Closed Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. No Significant Differences Were Observed.

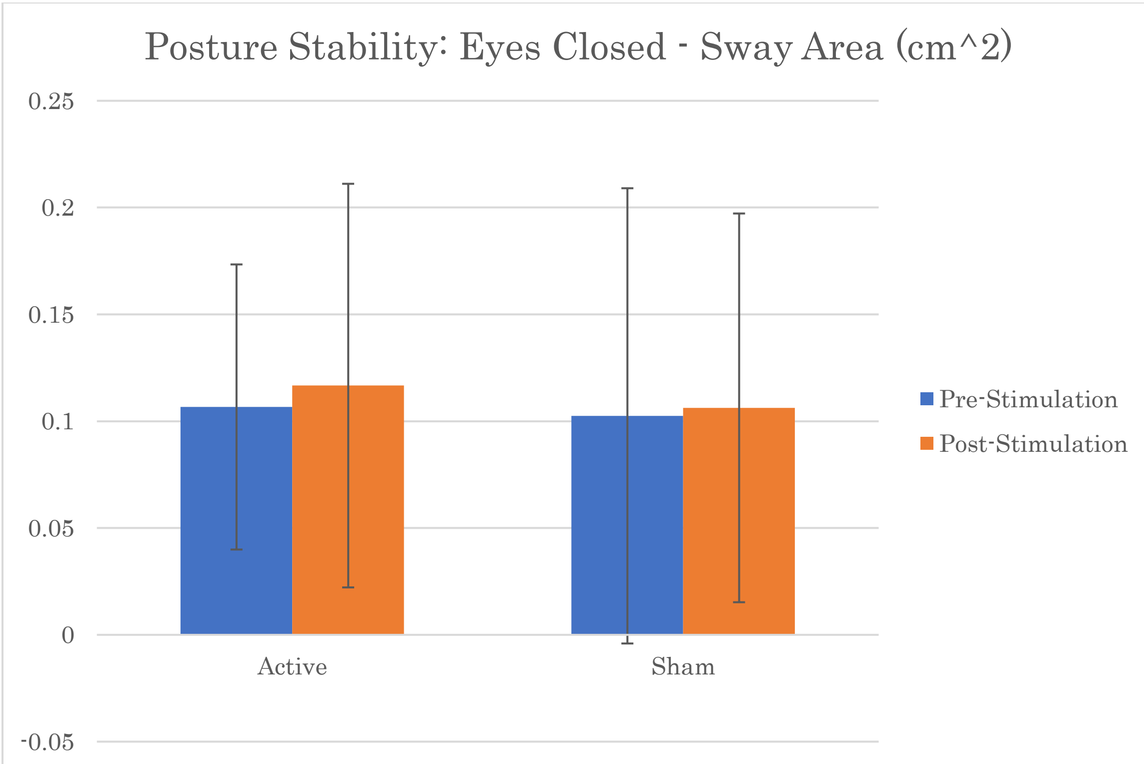

Figure 9. Average Values of Sway Area in the Eyes Closed Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. No Significant Differences Were Observed.

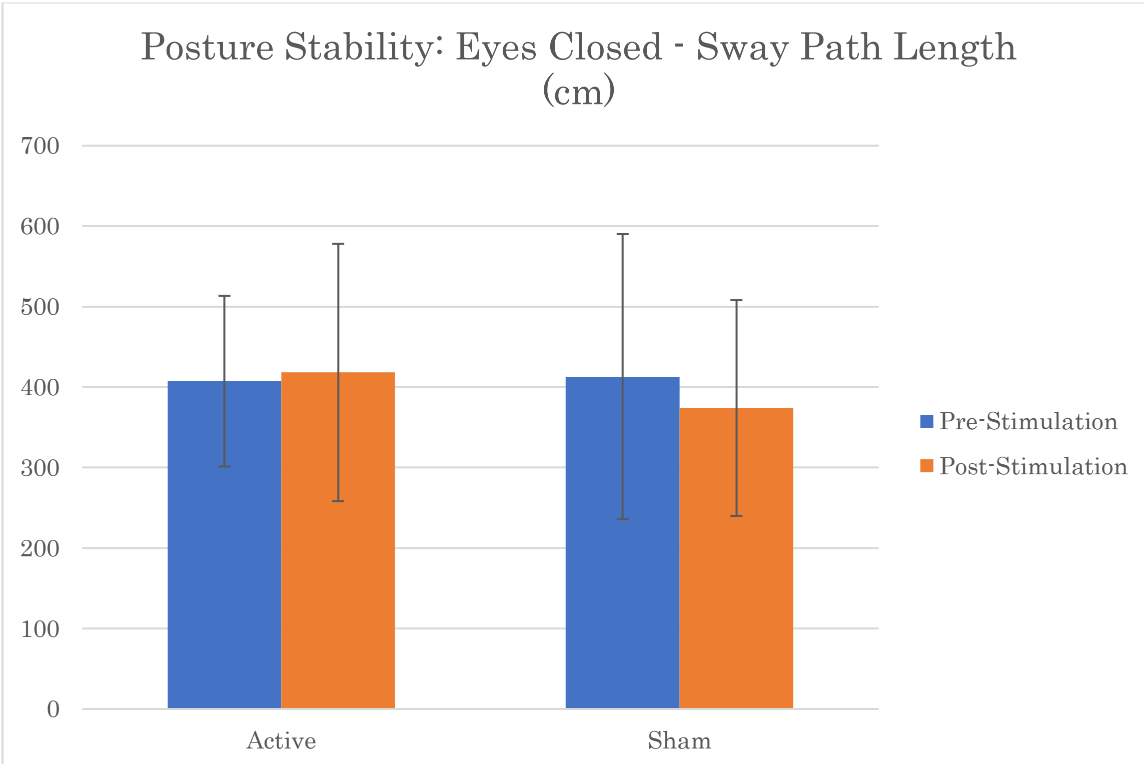

Figure 10. Average Values of Sway Path Length in the Eyes Closed Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. No Significant Differences Were Observed.

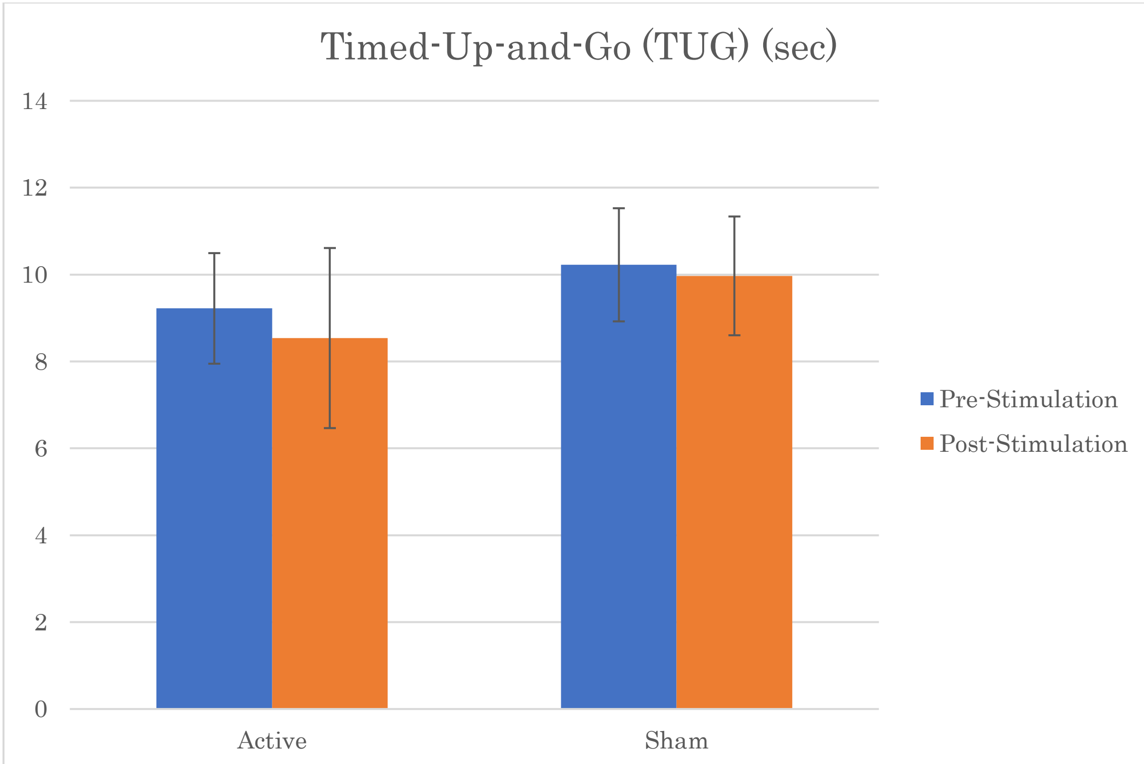

Figure 11. Average Values of Timed-Up-and-Go (TUG) Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. No Significant Differences Were Observed.

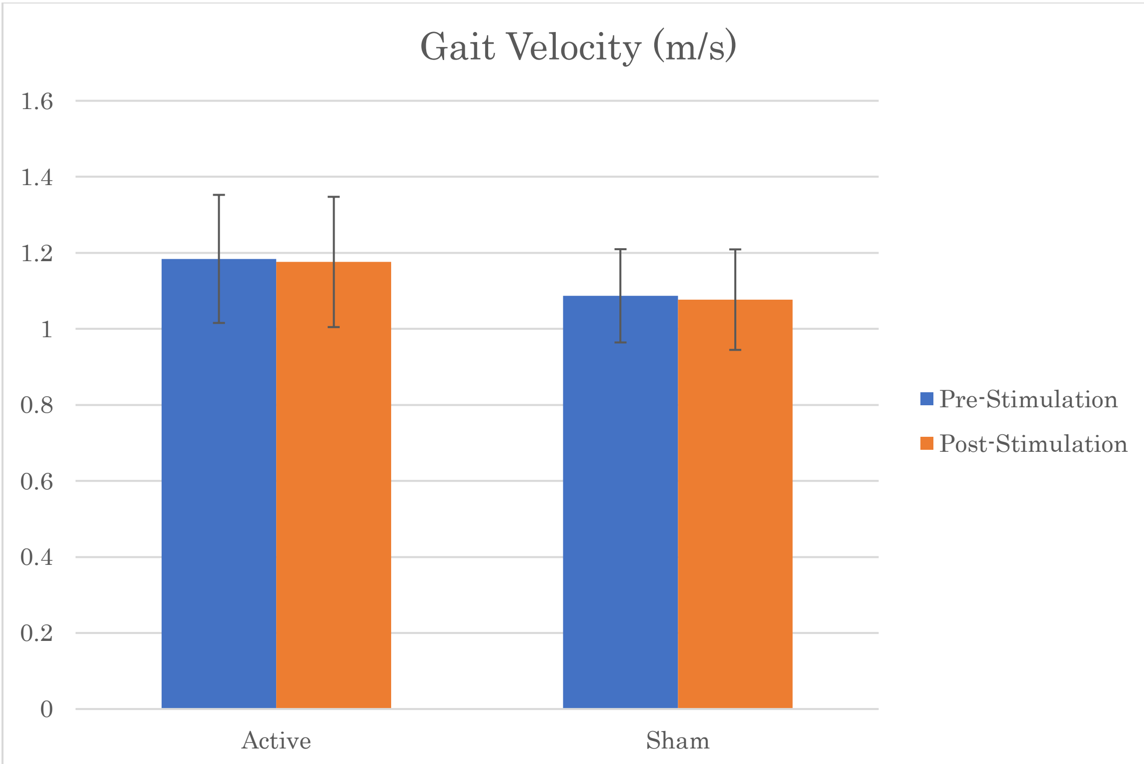

Figure 12. Average Values of the Gait Velocity Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. No Significant Differences Were Observed.

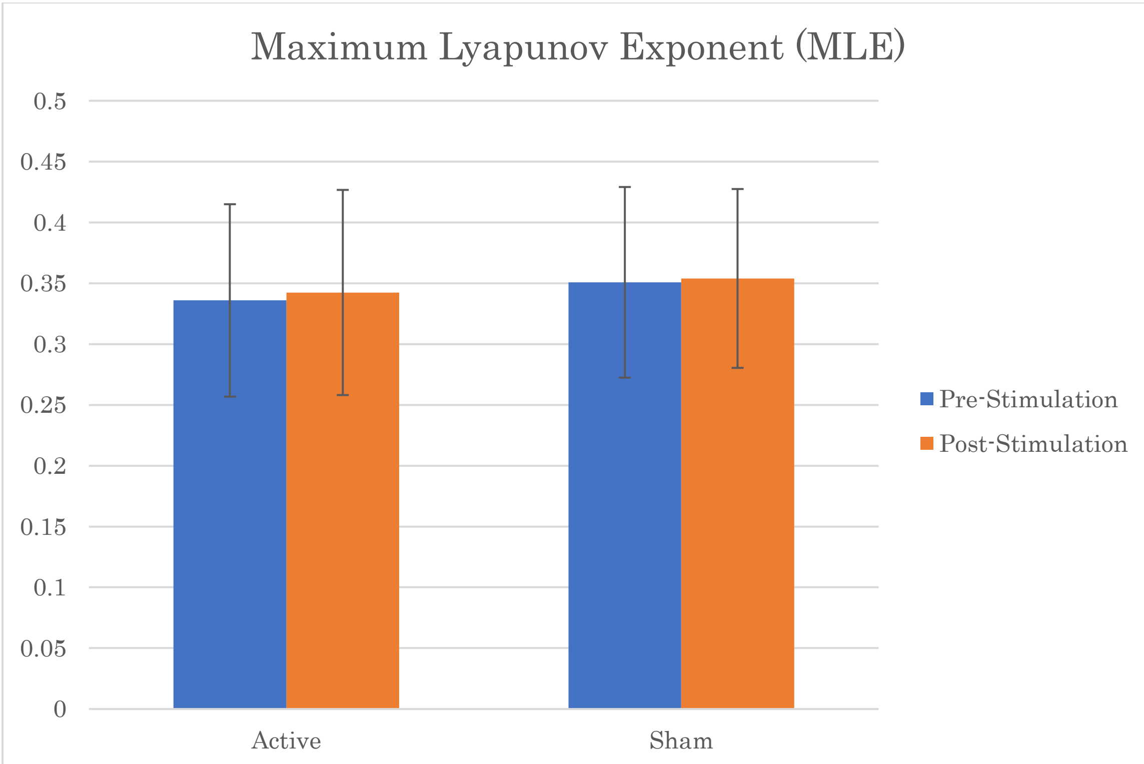

Figure 13. Average Values of the Maximum Lyapunov Exponent (MLE) Trial for the Active and Sham Groups Both Pre and Post Stimulation. Error Bars Represent Standard Deviation. No Significant Differences Were Observed.

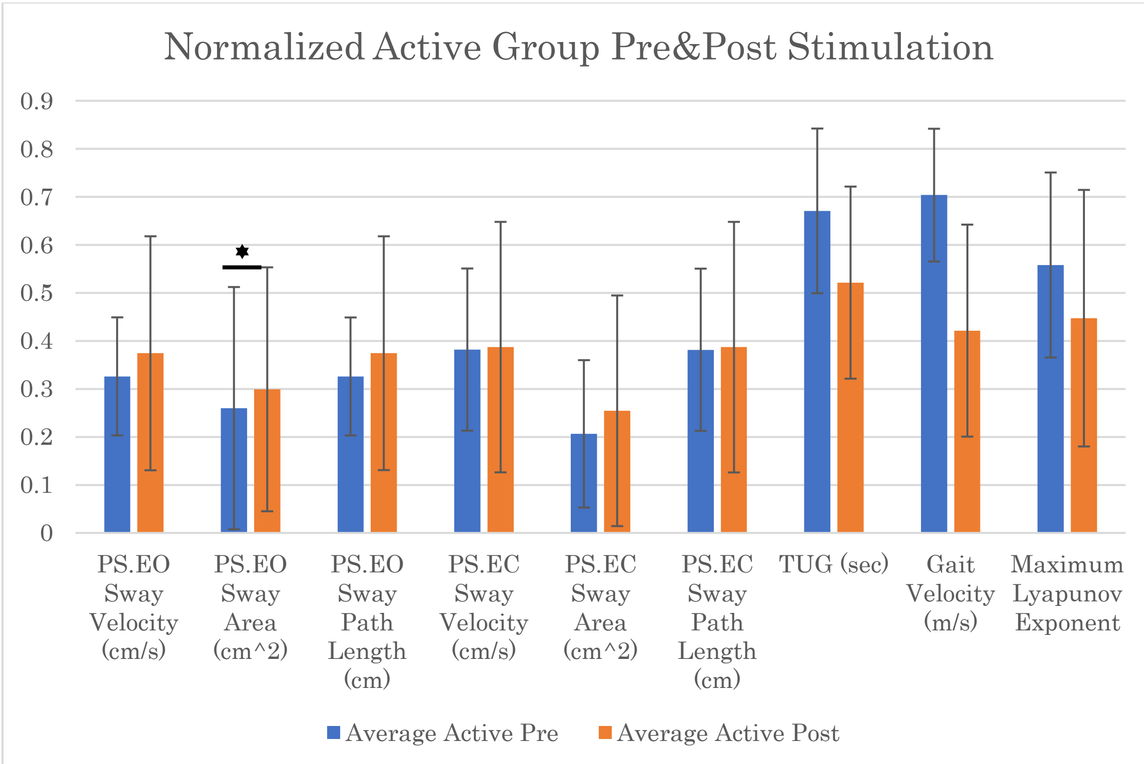

Figure 14. Average Normalized Values All Trials for the Active Group Both Pre and Post Stimulation. Error Bars Represent Standard Deviation of the Normalized Data. Significant Differences Were Observed Between the Pre and Post Stimulation in the Active Group for the Eyes Open Sway Area Metric with a P-value Of .023.

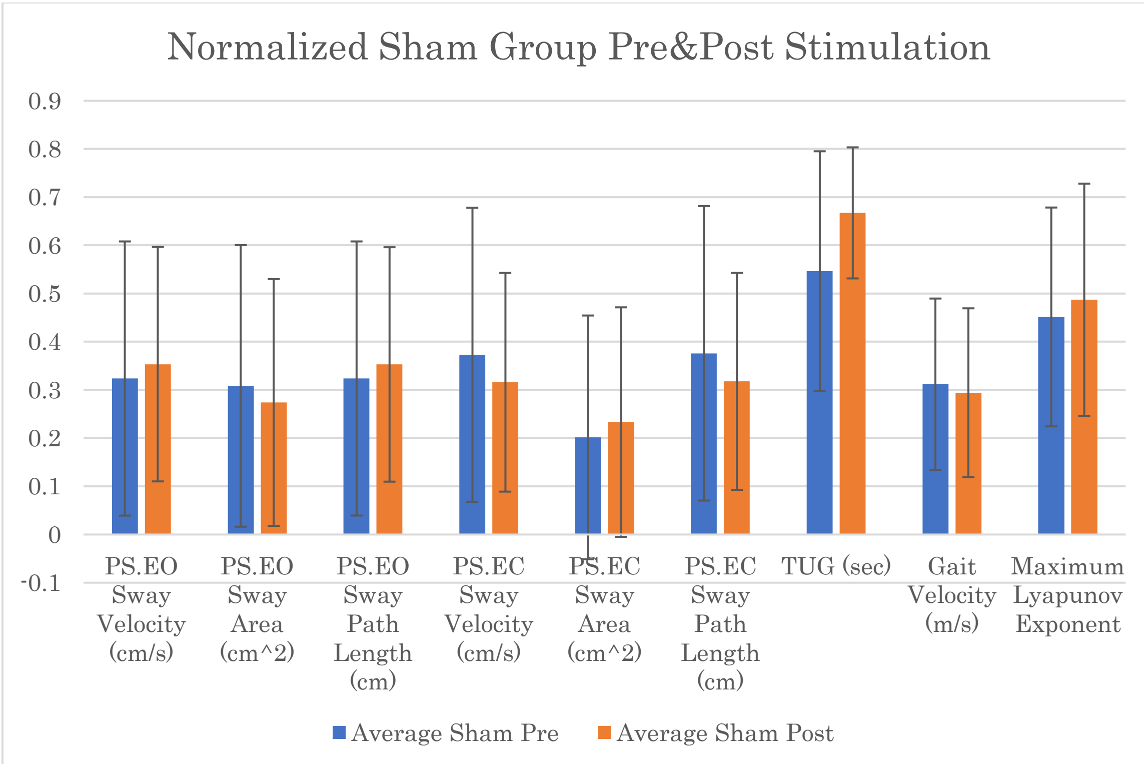

Figure 15. Average Normalized Values All Trials for the Sham Group Both Pre and Post Stimulation. Error Bars Represent Standard Deviation of the Normalized Data. No Significant Differences Were Observed.

DISCUSSION

Since significant differences were only observed in one of the nine metrics measured in this study, it is reasonable to conclude that Cervical Nerve Stimulation does not create a significant difference in acute balance and postural stability metrics in healthy adults. Several explanations could account for the results observed in this trial. One possible explanation for the lack of acute effect is the transient nature of the effects of CNS. According to one study, the side effects of electrical nerve stimulation are often associated with the "on" phase of the implantable device and have little to no effect on balance, usually manifesting in more proximal regions of the body to the stimulation device (Ben-Menachem). This study focused on implantable VNS devices, and showed only minor side effects such as coughing, hoarseness, voice alterations, and paresthesia, or "pins and needles", and did not show any signs of psychomotor slowing (Ben-Menachem). Currently, there are several studies in progress analyzing the effects of VNS on athletic performance, which may show differing results due to the level of stress under which the subject is during the given task. Since TENS targeting cranial nerves is known to activate the noradrenergic system and a parasympathetic nervous response, the level of stress can also play an important role in determining the effects. In the theory of optimal arousal, also known as the Yerkes-Dodson law, performance level increases with increased mental or physiological arousal up to a certain point, at which point increased arousal will cause a decrease in performance (*Classics in the History of Psychology -- Yerkes & Dodson (1908)*). With low arousal, little interest is invested in a task, and the subject will perform carelessly. As arousal increases, a subject will be more attentive and engaged in the action, thereby performing better. If the mental or physiological arousal is past the optimal level, the anxiety associated with it will begin to decrease the subject's performance. With regard to athletic performance, it is theorized that TENS in targeted cranial nerves may be able to decrease the increased stress levels of an athlete back to an optimal level for better performance. However, this study was performed on healthy individuals performing very basic tasks such as maintaining posture, sitting, standing, and walking, which are extremely low stress, causing a lack of change and in some cases decreased stability trends in some subjects. The autonomous form of walking described earlier may not have been influenced by the stimulation based of the degree of separation between the stimulation and brain control structures, whereas in a population where basic movement such as walking would fall into the more cognizant form of gait and were the source of stress. Patients with lower extremity difficulties and Parkinson's may benefit from the stimulation of these pathways through the cervical region and prove to yield a return to more normal gait patterns and a relatively increased stability.

An additional theory for the lack of adjustment in fall risk metrics is the theory that excluding a major change in physiology or brain function, a person's internal brain control mechanism of stability is very resistant to acute changes and will not be significantly altered by changing one input such as TNS. Despite the lack of significance in these metrics, a deeper analysis using complexity may yield more insight into any effects TNS has on these metrics. Additionally, other methods of analysis of accelerometer data can be used to elicit a more robust value of the MLE, as described in Kreisler et al., 2018 (Kreisler et al.). Despite the lack of significant differences, it is important to note that no adverse events were reported in the active group, indicating the safety of the therapy for future testing on different populations.

CONCLUSION

After administering acute CNS to 31 healthy adult subjects, only one of the nine fall risk metrics showed statistically significant differences between the pre and post stimulation in the active group, while none showed statistically significant differences in the sham group. Due to the lack of significance, it can be concluded that CNS does not create a significant difference in these fall risk metrics in healthy adults, potentially due to the Yerkes-Dodson Law, analysis methods, or the degree of separation between brain control structure and nerve stimulation. The treatment was proven to be safe based on no adverse reports in the follow-up data in the active group.

REFERENCES

Abarbanel, Henry D. I. *Analysis of Observed Chaotic Data*. Springer-Verlag, 1996. *www.springer.com*, //www.springer.com/us/book/9780387983721.

---. "The Analysis of Observed Chaotic Data in Physical Systems." *Reviews of Modern Physics*, vol. 65, no. 4, Oct. 1993, pp. 1331–92. *APS*, doi:10.1103/RevModPhys.65.1331.

Alexander, B. H., et al. "The Cost and Frequency of Hospitalization for Fall-Related Injuries in Older Adults." *American Journal of Public Health*, vol. 82, no. 7, July 1992, pp. 1020–23.

Ben-Menachem, E. "Vagus Nerve Stimulation, Side Effects, and Long-Term Safety." *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society*, vol. 18, no. 5, Sept. 2001, pp. 415–18.

Berridge, C. W., and R. C. Spencer. "Chapter 4 - Noradrenergic Control of Arousal and Stress." *Stress: Neuroendocrinology and Neurobiology*, edited by George Fink, Academic Press, 2017, pp. 39–47. *ScienceDirect*, doi:10.1016/B978-0-12-802175-0.00004-8.

Cerebellum (Section 3, Chapter 5) Neuroscience Online: An Electronic Textbook for the Neurosciences | Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston. https://nba.uth.tmc.edu/neuroscience/m/s3/chapter05.html. Accessed 4 Apr. 2019.

Classics in the History of Psychology -- Yerkes & Dodson (1908). http://psychclassics.yorku.ca/Yerkes/Law/. Accessed 27 Mar. 2019.

Cook, Ian A., et al. "Trigeminal Nerve Stimulation for Comorbid Posttraumatic Stress Disorder and Major Depressive Disorder." *Neuromodulation: Journal of the International Neuromodulation Society*, vol. 19, no. 3, Apr. 2016, pp. 299–305. *PubMed*, doi:10.1111/ner.12399.

DeGiorgio, Christopher M., et al. "Randomized Controlled Trial of Trigeminal Nerve Stimulation for Drug-Resistant Epilepsy." *Neurology*, vol. 80, no. 9, Feb. 2013, pp. 786–91. *n.neurology.org*, doi:10.1212/WNL.0b013e318285c11a.

Dingwell, Jonathan B., and Laura C. Marin. "Kinematic Variability and Local Dynamic Stability of Upper Body Motions When Walking at Different Speeds." *Journal of Biomechanics*, vol. 39, no. 3, 2006, pp. 444–52. *PubMed*, doi:10.1016/j.jbiomech.2004.12.014.

England, Scott A., and Kevin P. Granata. "The Influence of Gait Speed on Local Dynamic Stability of Walking." *Gait & Posture*, vol. 25, no. 2, Feb. 2007, pp. 172–78. *PubMed Central*, doi:10.1016/j.gaitpost.2006.03.003.

Florence Curtis S., et al. "Medical Costs of Fatal and Nonfatal Falls in Older Adults." *Journal of the American Geriatrics Society*, vol. 0, no. 0, Mar. 2018. *onlinelibrary.wiley.com (Atypon)*, doi:10.1111/jgs.15304.

Frangos, Eleni, and Barry R. Komisaruk. "Access to Vagal Projections via Cutaneous Electrical Stimulation of the Neck: FMRI Evidence in Healthy Humans." *Brain Stimulation*, vol. 10, no. 1, Jan. 2017, pp. 19–27. *ScienceDirect*, doi:10.1016/j.brs.2016.10.008.

Froude Number. https://www.engineeringtoolbox.com/froude-number-d_578.html. Accessed 13 Feb. 2018.

Group Differences among Fall-Prone Individuals and Healthy Old and Younger Counterparts Utilizing Nonlinear Stability Measures - Journal of Biomechanics. http://www.jbiomech.com/article/S0021-9290(06)83251-3/abstract. Accessed 8 Apr. 2018.

Howland, Robert H. "Vagus Nerve Stimulation." *Current Behavioral Neuroscience Reports*, vol. 1, no. 2, June 2014, pp. 64–73. *PubMed Central*, doi:10.1007/s40473-014-0010-5.

Important Facts about Falls | Home and Recreational Safety | CDC Injury Center. 12 Mar. 2018, https://www.cdc.gov/homeandrecreationalsafety/falls/adultfalls.html.

Kreisler, Itai Goeta, et al. "The Effects of Perturbation on Dynamic Stability for Fall Risk Analysis." *Barrett, The Honors College Thesis/Creative Project Collection*, 2018. *repository.asu.edu*, http://hdl.handle.net/2286/R.I.48098.

Lanciego, José L., et al. "Functional Neuroanatomy of the Basal Ganglia." *Cold Spring Harbor Perspectives in Medicine*, vol. 2, no. 12, Dec. 2012. *PubMed Central*, doi:10.1101/cshperspect.a009621.

Leipholz, Horst. *Stability Theory: An Introduction to the Stability of Dynamic Systems and Rigid Bodies*. 2nd ed., Vieweg+Teubner Verlag, 1987. *www.springer.com*, //www.springer.com/gb/book/9783519021056.

Liu, Jian, et al. "Fall Risk Assessments Based on Postural and Dynamic Stability Using Inertial Measurement Unit." *Safety and Health at Work*, vol. 3, no. 3, Sept. 2012, pp. 192–98. *PubMed Central*, doi:10.5491/SHAW.2012.3.3.192.

Lockhart, Thurmon E., and Jian Liu. "Differentiating Fall-Prone and Healthy Adults Using Local Dynamic Stability." *Ergonomics*, vol. 51, no. 12, Dec. 2008, pp. 1860–72. *PubMed Central*, doi:10.1080/00140130802567079.

Maki, Brian E. "Gait Changes in Older Adults: Predictors of Falls or Indicators of Fear?" *Journal of the American Geriatrics Society*, vol. 45, no. 3, 1997, pp. 313–20. *Wiley Online Library*, doi:10.1111/j.1532-5415.1997.tb00946.x.

Maruyama, Tetsuhiro, and Nobuo Yanagisawa. "Cognitive Impact on Freezing of Gait in Parkinson's Disease." *Parkinsonism & Related Disorders*, vol. 12, Oct. 2006, pp. S77–82. *ScienceDirect*, doi:10.1016/j.parkreldis.2006.05.024.

McGough, James J., et al. "An Eight-Week, Open-Trial, Pilot Feasibility Study of Trigeminal Nerve Stimulation in Youth with Attention-Deficit/Hyperactivity Disorder." *Brain Stimulation*, vol. 8, no. 2, Apr. 2015, pp. 299–304. *PubMed*, doi:10.1016/j.brs.2014.11.013.

Melzer, I., et al. "Postural Stability in the Elderly: A Comparison between Fallers and Non-Fallers." *Age and Ageing*, vol. 33, no. 6, Nov. 2004, pp. 602–07. *academic.oup.com*, doi:10.1093/ageing/afh218.

Ogbonnaya, Sunny, and Chandrasekaran Kaliaperumal. "Vagal Nerve Stimulator: Evolving Trends." *Journal of Natural Science, Biology, and Medicine*, vol. 4, no. 1, 2013, pp. 8–13. *PubMed Central*, doi:10.4103/0976-9668.107254.

O'Loughlin, J. L., et al. "Incidence of and Risk Factors for Falls and Injurious Falls among the Community-Dwelling Elderly." *American Journal of Epidemiology*, vol. 137, no. 3, Feb. 1993, pp. 342–54.

Parijat, Prakriti, et al. "Effects of Perturbation-Based Slip Training Using a Virtual Reality Environment on Slip-Induced Falls." *Annals of Biomedical Engineering*, vol. 43, no. 4, Apr. 2015, pp. 958–67. *PubMed*, doi:10.1007/s10439-014-1128-z.

Practical Method for Determining the Minimum Embedding Dimension of a Scalar Time Series - ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0167278997001188. Accessed 17 Apr. 2018.

Rezvanian, Saba, and Thurmon E. Lockhart. "Towards Real-Time Detection of Freezing of Gait Using Wavelet Transform on Wireless Accelerometer Data." *Sensors (Basel, Switzerland)*, vol. 16, no. 4, Apr. 2016. *PubMed*, doi:10.3390/s16040475.

Rosano, Caterina, et al. "Quantitative Measures of Gait Characteristics Indicate Prevalence of Underlying Subclinical Structural Brain Abnormalities in High-Functioning Older Adults." *Neuroepidemiology*, vol. 26, no. 1, 2006, pp. 52–60. *www.karger.com*, doi:10.1159/000089240.

Soss, Jason, et al. "A Prospective Long-Term Study of External Trigeminal Nerve Stimulation for Drug-Resistant Epilepsy." *Epilepsy & Behavior*, vol. 42, Jan. 2015, pp. 44–47. *ScienceDirect*, doi:10.1016/j.yebeh.2014.10.029.

Stevens, Judy A., et al. "Gender Differences in Seeking Care for Falls in the Aged Medicare Population." *American Journal of Preventive Medicine*, vol. 43, no. 1, July 2012, pp. 59–62. *PubMed*, doi:10.1016/j.amepre.2012.03.008.

Takakusaki, Kaoru. "Functional Neuroanatomy for Posture and Gait Control." *Journal of Movement Disorders*, vol. 10, no. 1, Jan. 2017, pp. 1–17. *PubMed Central*, doi:10.14802/jmd.16062.

"Takens's Theorem." *Wikipedia*, 16 Feb. 2018. *Wikipedia*, https://en.wikipedia.org/w/index.php?title=Takens%27s_theorem&oldid=826003231.

The Emerging Use of Technology for the Treatment of Depression and Other Neuropsychiatric Disorders. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/21318196. Accessed 25 Mar. 2019.

The Impact of Preinjury Anticoagulants and Prescription Antiplatelet Agents on Outcomes in Older Patients with Traumatic Brain Injury | Ovid. https://oce.ovid.com/article/01586154-201402000-00025/HTML. Accessed 14 Mar. 2019.

Tsang, E. W., et al. "Involvement of the Human Pedunculopontine Nucleus Region in Voluntary Movements(e–Pub Ahead of Print)." *Neurology*, vol. 75, no. 11, Sept. 2010, pp. 950–59. *PubMed Central*, doi:10.1212/WNL.0b013e3181f25b35.

Tyler, William J., et al. "Transdermal Neuromodulation of Noradrenergic Activity Suppresses Psychophysiological and Biochemical Stress Responses in Humans." *Scientific Reports*, vol. 5, no. 1, Nov. 2015. *Crossref*, doi:10.1038/srep13865.

"Vagus Nerve Stimulation as a Novel Treatment Strategy for Parkinson's Disease." *MDS Abstracts*, https://www.mdsabstracts.org/abstract/vagus-nerve-stimulation-as-a-novel-treatment-strategy-for-parkinsons-disease/. Accessed 7 Mar. 2019.

Vellas, B. J., et al. "Fear of Falling and Restriction of Mobility in Elderly Fallers." *Age and Ageing*, vol. 26, no. 3, May 1997, pp. 189–93.

Walsh, Deirdre M. "The Evolution of Tens." *Hong Kong Physiotherapy Journal*, vol. 21, no. 1, 2003, pp. 1–4. *Crossref*, doi:10.1016/S1013-7025(09)70033-8.

Winn, Philip. "Mesopontine Tegmentum." *Encyclopedia of Neuroscience*, edited by Marc D. Binder et al., Springer Berlin Heidelberg, 2009, pp. 2340–43. *Springer Link*, doi:10.1007/978-3-540-29678-2_3449.

ZABARA, J. "Peripheral Control of Hypersynchonous Discharge in Epilepsy." *Electroencephalogr Clin Neurophysiol*, vol. 61, 1985, p. S162.