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Potential Benefits and Withdrawal Effects of Cranial Nerve Non-invasive Neuromodulation on Functional Mobility for Individuals with Traumatic Brain Injury

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POTENTIAL BENEFITS AND WITHDRAWAL EFFECTS OF CRANIAL NERVE
NON-INVASIVE NEUROMODULATION ON FUNCTIONAL MOBILITY FOR
INDIVIDUALS WITH TRAUMATIC BRAIN INJURY

by

Kati P. Liegl

A Thesis Submitted in
Partial Fulfillment of the
Requirements for the Degree of

Master of Science
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at

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December 2013

ABSTRACT

POTENTIAL BENEFITS AND WITHDRAWAL EFFECTS OF CRANIAL NERVE NON-INVASIVE NEUROMODULATION ON FUNCTIONAL MOBILITY FOR INDIVIDUALS WITH TRAUMATIC BRAIN INJURY

by

Kati P. Liegl

The University of Wisconsin-Milwaukee, 2013
Under the Supervision of Roger O. Smith

Objective: Document and describe benefits and withdrawal effects of the Cranial Nerve Non-Invasive Neuromodulation (CN-NINM) intervention.

Background: Neuromodulation techniques can be used for the treatment of many diagnoses and conditions. Many current neuromodulation techniques have or can have negative consequences such as high cost, risk of surgical complications or infections, effects not lasting without the drug or stimulation presence, and need for medical experts' direct oversight. A new rehabilitation intervention called CN-NINM may eliminate these negative factors, making it a promising tool for clinicians and participants. CN-NINM combines targeted training activities with mild, portable, electrical stimulation of the tongue to facilitate learning. It was created after repeated clinical observations and functional improvements were noted in related research. However, a great deal is not known about the intervention mechanisms. To date, no negative consequences have been documented.

Methods: An A-B-A-B-A single case experimental design five week intensive protocol was implemented with one participant with a TBI. Seven measures were collected including the Timed Up and Go, Romberg, Sharpened Romberg, 4 components of the Dynamic Gait Index, 5 components of the Community Balance & Mobility Scale, Gait Efficacy Scale-modified, Community Integration Questionnaire, and Participation Objective, Participation Subjective.

Results: While several assessments suggested improved function over the study period, quantitative measures did not demonstrate statistically significant improvement across phases of the study. No quantitative decline in functional gait was evident during withdrawal phases. The participant reported improvements during intervention weeks, including reduced tone and pain, increased gait confidence, and increased activity tolerance.

Conclusion: CN-NINM warrants additional research. While this study demonstrated no statistically significant effects during either intervention or withdrawal phases, several qualitative observations suggest that the intervention can potentially provide fast results with little to no risk and comparatively small cost. Further research should involve multiple individuals with a number of repeated baseline and outcome measures sufficient to attain pre- and post-treatment stability.

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PART I: THESIS OVERVIEW AND PERSONAL REFLECTIONS

Overview of thesis organization

This thesis is comprised of three parts: Part I: Thesis Overview, Part II: Research Manuscript, and Part III: Appendices. Part I provides an overview of the thesis, timeline of the study, and lessons learned along the process. Part II includes the research manuscript. This manuscript contains background, methods, results, and conclusions sections. The research manuscript was prepared using guidelines for the Open Journal of Occupational Therapy. Part III consists of seven appendices related to the manuscript and overall thesis.

Timeline of the Study

The following is a chronological summary of the study. The CN-NINM intervention was introduced to the primary researcher in September 2011. Meetings to discuss study options and designs were completed throughout the summer of 2012. In September 2012, the primary researcher met with the research team at the Tactile Communication & Neurorehabilitation Laboratory at the University of Wisconsin Madison to discuss the fit of the proposed study into the research they had completed and to learn about any areas they were interested in gaining pilot data. On October 11, 2012, the primary researcher proposed the thesis to a committee of advisors. The committee members approved the design and hypotheses. On October 17, 2012, documents were submitted to the Institutional Review Board (IRB) for a full board review. After several iterations, IRB granted study approval on December 12 2012. IRB amendments were submitted in April and September 2013 for edits in study location and location of data storage.

Participant recruitment was open and active from December 12, 2012 until September 2013. During this time, multiple presentations were provided to targeted groups (Dryhooch, support groups, the VA/VFW, MCW etc...) in an attempt to recruit participants. Many more emails and phone calls were made trying to gain access to appropriate potential participants. In May 2012, the first and only participant to meet eligibility criteria completed all the assessments that would be completed during the study as exposure to the assessments. The participant began the full protocol on June 3rd and finished on July 5th. Two trained raters rated the data in October. The primary researcher received a College of Health Sciences Research Grant which provided compensation to the primary rater and compensation of supplies to the primary researcher. Over the course of the study, the primary researcher also presented the study design, PoNS™ device, and study results at national, state, and local presentations.

Summary of Changes

The original research protocol changed in three ways during implementation. First, although four participants were targeted to complete the study, only one participant was recruited that was eligible for and completed the study. Second, the participant completed a modified set of measures resulting in the Timed Up and Go, Romberg, Sharpened Romberg, components of the Dynamic Gait Index, and components of the Community Balance & Mobility Scale instead of only completing the Community Balance & Mobility Scale. This modification was included after the participant experienced lasting pain when completing the Community Balance & Mobility Scale on the first day, prior to

beginning the protocol. The participant attributed the pain to the orthopedic injuries and completing tasks he had previously tried to avoid. A third modification to the initial proposal was the completion of the entire study at IndependenceFirst instead of at the University of Wisconsin Milwaukee. Due to the change in location, the daily assessments were videotaped instead of being completed by a blinded assessor. A researcher unfamiliar with the study design later rated the videos with a second rater scoring 40% of the data to evaluate inter-rater reliability. All other protocols and procedures remained true to the proposal.

Learning Process

Over the course of the year and a half study, I have learned many things about research and the research process as well as about myself. These include a better understanding of the strengths and limitations of single case design research; the importance and difficulties of each step in the research process including creating a practical and exhaustive plan, word choice appropriate for IRB, and strategies for participant recruitment; as well as experience disseminating results that did not show the expected changes.

Single Case Design Characteristics

Single Case Design (SCD) studies are conceptualized, implemented, and evaluated very differently than group studies. While planning the study design, it became evident how important asking the right question and selecting the right design was. Initially, I often mixed designs, asking a SCD question but trying to design a group study to answer it. Over the course of several discussions, I

began to differentiate between group and SCD questions. As an occupational therapy student, I was very interested in my participants' experiences and the changes they noted. I was concerned with the process of the intervention which is documented throughout SCDs as opposed to a single pre-post assessment more typical to a group design. Small single case studies are essential to test the design of valid group studies. The lack of published research on the topic I chose makes the area a great fit for smaller, more customizable studies in order to inform a more effective group design and be best able to understand the interventions.

While initiating the study and throughout the study, I learned the value of the flexible design and structures of SCDs without losing treatment integrity. When my participant was unable to complete the study assessment as I had intended, I was able to modify the study before it began to allow him to participate. Days when the participant was tired, distracted, or not his typical self, I was able to discuss what was happening with him and make a note of the situation to explain the data variability. With group designs, these data points could be considered outliers and potentially be removed from the data set. In addition, I was able to record the participant's responses, reactions, and progress through the study. Although the dependent variable results did not fully support my hypotheses, I gained valuable information about the participant's experience and how a subsequent study might be better structured. Group designs often lack this personalized and detailed information.

The flexibility of the SCD was beneficial for my study, however, I also realized some of the limitations of SCD studies. The main limitation of all SCD studies is that although they provide detailed information about one participant's experiences, they provide no evidence that the pattern affects anyone else. Another limitation I experienced was related to the data analysis. With repeated measures and SCDs, visual analyses are standard. With data that clearly presents as the same or different across phases, this can be easy, efficient, and supported by statistical techniques. There are several techniques that are utilized to evaluate and understand repeated measures data. Examples include using the last three data points from each phase so there is a greater chance of phase stability, using two standard deviation band methods, or split middle celeration lines. My data did not fit well into typical data analysis methods. For example, one analysis method I completed was percentage of data overlap and I evaluated the Percentage of Data Exceeding the Median, Percentage of Data Exceeding the Mean, Non-pairwise Data Overlap, and Percentage Non-overlapping Data. On several graphs, the percentages seemed to indicate a difference in phases, however, by visually examining the data, there was no difference in phases. Other graphs had a 0% difference with several overlap techniques but 100% difference on one technique. This made it difficult to determine what was significant and representative of my data.

General Research Practice Guidelines

My thesis has helped me to better understand general research guidelines in addition to SCDs. I learned the value of well-constructed and very thorough

plans. I also learned the value of flexibility and being able to adapt under multiple circumstances. There were several instances that required me to plan future steps of the study. Each time I was faced with planning out details of the study I took it more seriously, was better able to understand the importance of the plans, and learned how to better anticipate what might happen in order to prepare contingency plans. I learned to appreciate a well-constructed and extensive plan and be better able at producing it. However, I also learned to adapt and make the most out of unforeseen situations while preserving as much treatment integrity as possible. This was necessary when the participant was unable to complete the intended assessment prior to beginning the study and when the participant was not able to be assessed one Friday during a withdrawal week, and instead was assessed before the intervention on the following Monday.

This study involved significant effort to obtain IRB approval and taught me a great deal about the IRB process. My study required a full board review and several iterations before being accepted. Through this process I learned about clear, concise writing, which is a challenge to me that I am slowly becoming more competent at, safety concerns from a participant and data perspective, and had the importance of carefully crafted plans re-emphasized.

Recruitment was a long, strenuous process throughout the study. During this process, I learned to leave my comfort zone, often, to be persistent, passionate, and memorable so people will remember my name or topic when I call back, and to network everywhere I go. Recruitment was the most difficult and frustrating component of my study, but also provided a great deal of learning

about myself and research. An important lesson I learned was to work with groups that you have access to before you begin the study.

I have learned and am continuing to learn a great deal about disseminating my information; many of these lessons overlap with those I learned in recruitment. I have presented at national, state, and local conferences and events and continue to be avid about presenting the work that I did. I was also not accepted to several national conferences which has taught me the importance of persistence and not letting frustration or rejections stop me from submitting my work again elsewhere. Over the course of my presentations, I have become more competent presenting my information logically, verbally conveying information to people, accepting criticism, and being persistent. I have learned the benefit of networking and stepping outside my comfort zone.

The last thing I learned was that research does not always go or end the way you want. Unanticipated results are not a sign of failure and do not necessarily indicate that the study found nothing of value. Although I was disappointed that the data looked nothing like I had anticipated, I also was able to learn a lot about the intervention process, research process, and additional ways to maintain higher treatment integrity.

PART II: RESEARCH MANUSCRIPT

Abstract

Objective: Document and describe benefits, withdrawal effects and experience with the Cranial Nerve Non-Invasive Neuromodulation (CN-NINM) intervention.

Background: Neuromodulation techniques can be used for the treatment of many diagnoses and conditions. Many current neuromodulation techniques have or can have negative consequences such as high cost, risk of surgical complications or infections, effects not lasting without the drug or stimulation presence, and need for medical experts' direct oversight. A new rehabilitation intervention called CN-NINM may eliminate these negative factors, making it a promising tool for clinicians and participants. CN-NINM combines targeted training activities with mild, portable, electrical stimulation of the tongue to facilitate learning. It was created after repeated clinical observations and functional improvements were noted in related research. However, a great deal is not known about the intervention mechanisms. To date, no negative consequences have been documented.

Methods: An A-B-A-B-A single case experimental design five week intensive protocol was implemented with one participant with a TBI. Seven measures were collected including the Timed Up and Go, Romberg, Sharpened Romberg, 4 components of the Dynamic Gait Index, 5 components of the Community Balance & Mobility Scale, Gait Efficacy Scale-modified, Community Integration Questionnaire, and Participation Objective, Participation Subjective.

Results: While several assessments suggested improved function over the study period, quantitative measures did not demonstrate statistically significant improvement across phases of the study. No quantitative decline in functional gait was evident during withdrawal phases. The participant reported improvements during intervention weeks, including reduced tone and pain, increased gait confidence, and increased activity tolerance.

Conclusion: CN-NINM warrants additional research. While this study demonstrated no statistically significant effects during either intervention or withdrawal phases, several qualitative observations suggest that the intervention can potentially provide fast results with little to no risk and comparatively small cost. Further research should involve multiple individuals with a number of repeated baseline and outcome measures sufficient to attain pre- and post-treatment stability.

Background

Therapeutic uses of neuromodulation is a relatively new field that is expanding in scope and prescription. Neuromodulation is the suppression or stimulation of the central or peripheral nervous system using pharmacological or electrical techniques. Common techniques seen in rehabilitation vary widely and can include baclofen pumps, deep brain stimulators, and transcranial magnetic stimulation. Several show promise in improving function and quality of life for users across many disabilities yet currently available techniques have several undesirable characteristics or consequences. The following brief summary highlights several of the limitations for current neuromodulation techniques.

Each technique presents different strengths and limitations. Intrathecal baclofen, or baclofen pumps, can be effective at reducing severe spasticity, particularly in traumatic brain injury (TBI), cerebral palsy, or spinal cord injuries (Awaad et al., 2012). Deep brain stimulators decrease tremors as well as rigidity, bradykinesia, and gait difficulties in participant's with Parkinson's Disease and has shown positive benefits to patients (Perlmutter & Mink, 2006). However, both are surgical interventions, introducing risks of infections and complications during surgery (Perlmutter & Mink, 2006; Weaver et al., 2009). Both require training on precautions and care of the devices. Maintenance or malfunctions require medical attention and can be costly (Awaad et al., 2012). In addition, both lack research documenting carry-over effects. The devices are intended for long term use and symptoms may return when the devices are not "on" (Cooper, McIntyre, Fernandez, & Vitek, 2013; Kern & Kumar, 2007).

Transcranial magnetic stimulation (TMS) is gaining popularity as treatment for depression that is unresponsive to conventional treatments; however, limitations are inherent in this as well. Each session requires medical expertise thereby increasing the cost. The intervention is unable to target specific, small structures or isolate deep structures, instead stimulating large areas of the brain. In some cases, repetitive TMS has had harmful side effects, such as seizures, in healthy participants (Cramer et al., 2011; O'Malley, Ro, & Levin, 2006).

Cranial Nerve Non-Invasive Neuromodulation (CN-NINM), a therapeutic intervention created in 2006 at the Tactile Communication & Neurorehabilitation Laboratory (TCNL) at the University of Wisconsin Madison, appears to avoid the limitations and risks of preceding techniques. CN-NINM, explained in detail below, uses non-surgical oral electrical stimulation through a participant controlled device paired with customized training activities, thereby avoiding the risks associated with surgeries and medical stays and potentially reducing the overall cost. CN-NINM requires an initial training period by a trained therapist, but participants can use the devices independently after demonstrating a satisfactory level of understanding of the intervention and device maintenance (TCNL, 2012). This independence reduces the overall costs of the intervention. If a device malfunctions, a new one can replace the old without additional therapy, training or treatment, and requires very limited expert time or participant interaction.

Although the stimulation is provided orally and does not stimulate specific targeted sections of the brain, the stimulation utilizes existing neural pathways, and changes noted in previous studies appear related to the trainings activities

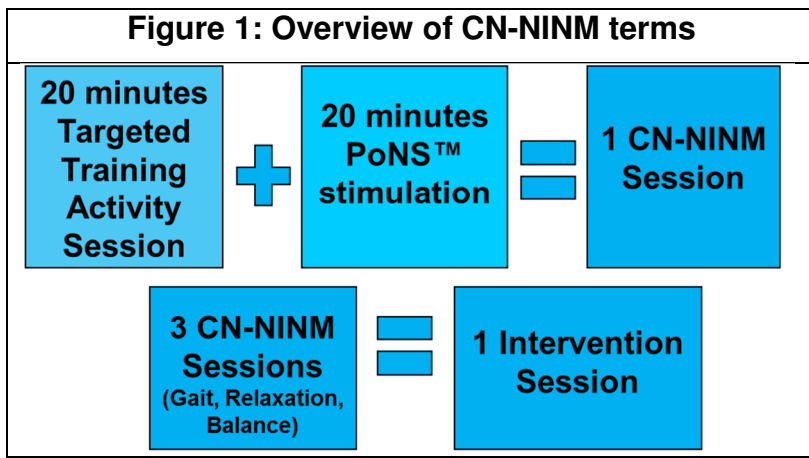
provided during the studies (TCNL, 2012). CN-NINM may prime the brain for learning and therefore specific results are targeted based on what is practiced during the intervention. Case reports lead researchers to believe CN-NINM may have lasting effects depending on the diagnosis and length of time using the intervention (TCNL, personal communication, 2012-2013). These benefits make CN-NINM a feasible complement to rehabilitation, particularly neurorehabilitation.

Cranial Nerve Non-Invasive Neuromodulation (CN-NINM)

The CN-NINM intervention and protocols were created after sensory substitution and biofeedback studies observed improved function that was not anticipated based on the treatment. During sensory substitution (Bach-y-Rita, Collins, Saunders, White, & Scadden, 1969; Bach-y-Rita, Kaczmarek, Tyler, & Garcia-Lara, 1998; Bach-y-Rita & Kercel, 2003) and electrical stimulation biofeedback work (Barros, Bittar, & Danilov, 2010; Danilov, Tyler, Skinner, Hogle, & Bach-y-Rita, 2007; Tyler, Danilov, & Bach-y-Rita, 2003), participants reported improvements in sleep, vision, coordination, mood, pain, concentration, balance and gait. These reports were not initially expected. A research team involved in both lines of work began to explore the effect of information-free oral electrical stimulation, (i.e. not used for sensory substitution or biofeedback) combined with targeted training activities (TCNL, 2012).

The CN-NINM intervention has two components: 1) Targeted Training Activity Sessions, combined simultaneously with 2) oral, electrical stimulation provided by the Portable Neuromodulation Stimulator (PoNS™) device to create

one CN-NINM session (See Figure 1). Each CN-NINM session is 20 minutes to maximize learning and functional gain (TCNL, 2012). Targeted Training Activity

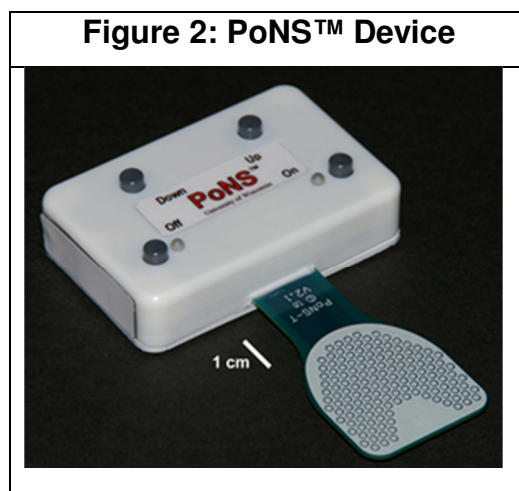


Sessions are individualized training sessions specific to the participant's goals and dependent on his/her abilities and limitations to provide the “just

right challenge” (Yerxa, 1990). For example, a participant with a balance impairment receives customized balance trainings, often utilizing yoga balls, balance foam, or challenging floor foot placements, depending on ability. Previous research has studied balance and gait; initial protocols included CN-NINM Sessions for balance, gait, and relaxation.

Portable Neuromodulation Stimulator (PoNS™) Device

The PoNS™ is a “T” shaped device (See Figure 2) with an oral tab slightly larger than a quarter that rests on the anterior third of the tongue. The device is held lightly in place by the lips and is small and light enough participants can complete other tasks while using it (See Figure 3).



Participants are always in charge of the device and stimulation intensity. (For

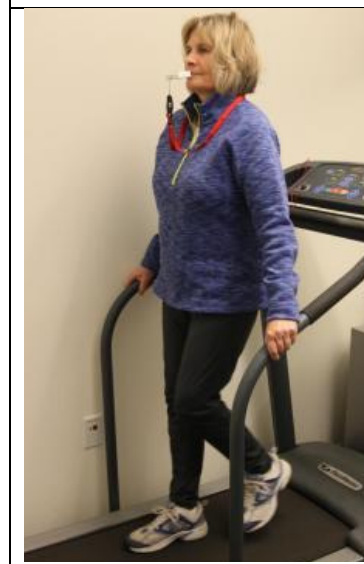
more detail on the PoNS™, see Appendix A.) The PoNS™ has not yet received Food and Drug Administration (FDA) approval, but it is FDA recognized as a nonsignificant risk device. Currently no negative effects have been reported from using the PoNS™.

The PoNS™ device provides oral stimulation based on the documented benefits and results of previous research (Fabien, Nicolas, Orliaguet, & Payan, 2007; Kaczmarek, 2011; Ptito, Moesgaard, Gjedde, & Kupers, 2005; Vuillerme & Cuisinier, 2009; Wildenberg, Tyler, Danilov, Kaczmarek, & Meyerand, 2010). In addition, the tongue provides access to branches of the trigeminal and facial cranial nerves (CN V and VII, respectively). The cranial nerves provide a figurative freeway into the brain and intersect the central nervous system in centers in the brainstem responsible for sensory integration and movement coordination (Twenty Eleven Theme, 2011).

Prior CN-NINM Research

CN-NINM has been tested in small studies across multiple diagnostic groups with balance and gait deficits. None of these studies have been published yet. All studies have had positive results. Individuals with chronic balance dysfunctions and TBIs demonstrated large, fast improvements in balance and gait tasks. Individuals with Multiple Sclerosis (MS) experienced gains in balance and gait tasks that took longer to observe. Although there have been randomized

Figure 3: Participant using the PoNS™ device during gait CN-NINM session



controlled trials, much of CN-NINM research is still exploratory (TCNL, personal communication, 2012-2013). Preliminary descriptive research is appropriate and informative for the design of later studies (Portney & Watkins, 2009). No journal articles have been published yet directly on the CN-NINM intervention. The following is a brief summary of three areas of study from prior research.

1. Chronic Balance Dysfunction

To better understand the changes in the brain, fMRI studies looked at the nine participants with chronic balance dysfunctions before and after 19 CN-NINM balance sessions. fMRI scans showed activations in the right vestibular nucleus, right superior colliculus, and multiple cerebellar structures. After the CN-NINM intervention, the right trigeminal nucleus, the origin site for neuromodulation in behavioral and subjective measures improvement, showed increased responses (Wildenberg, Tyler, Danilov, Kaczmarek, & Meyerand, 2011). After prolonged activation, the circuits can undergo neuronal reorganization, thus leading to an increased ability to learn or relearn tasks and demonstrating the brain's plasticity, which is also known to occur in the absence of neuromodulation.

Balance testing was also evaluated before and after the CN-NINM balance sessions. Seven participants had an improvement on the Sensory Organization Test (SOT) scores. Scores increased an average of 15.75 points (SE=5.59, $p=0.026$, paired Student's t-test) (Wildenberg et al., 2011) with changes greater than 8 points indicating a true change (Wrisley et al., 2007).

2. Multiple Sclerosis

During a two week, ten person pilot study on Multiple Sclerosis (MS), all ten participants showed clinically significant improvements on the Dynamic Gait Index (DGI), a clinical measure of functional gait quality (Huang et al., 2011). However, eight participants' functional levels returned to baseline after the study. After receiving additional funding, the participants were able to participate in a longitudinal study, and all the participants regained the improvements they had lost (Tyler, 2010).

Danilov and colleagues (N.D.) studied balance and gait changes from CN-NINM in a randomized controlled trial with twenty participants with MS randomly assigned to either the control or active group. The study consisted of an initial assessment of the DGI, two weeks of laboratory training followed by 12 weeks completed independently in the participant's home and additional DGI assessments at week 2, 6, 10 and 14. Each group received training activities to complete, the control group received a PoNS™ device that provide stimulation too light to detect and the active group received a PoNS™ device that provided detectable stimulation controllable by the participant. All participants completed the study. By the end of the two week laboratory training, the experimental group reached twice the improvement on the DGI than the control group. At 10- and 14-week assessments, the difference between groups was statistically significant. At the 10 week assessment, the active group reached 80% improvement; the control group reached 40% improvement. This is a difference of four points of improvement on the raw score. Scores for the active group improved slightly at

week 14 and decreased for the control group. Analysis of the groups showed the only difference in group demographics was the length of time since diagnosis of MS; the experimental group generally had a longer time since diagnosis.

Typically, a longer time would suggest poorer functioning, however, in this study, the participants performed significantly better on the DGI (Danilov et al., N.D.).

3. Traumatic Brain Injury Case Studies

Two individuals with TBIs greater than 5 years prior used the CN-NINM intervention in a pilot study. Both had had concussive, non-penetrating injuries. Participants completed a 2-week protocol, five days per week. The DGI and SOT were assessed before and after the 2-week session. Each participant had clinically improved scores on both, with DGI scores improving from 10 to 24 for one participant and 9 to 23 for the other. SOT composite scores increased from 55 to 77 and from 41 to 88. In addition, the participants reported improved memory and mood elevation (Danilov et al., 2013).

Both participants saw improvements from the CN-NINM intervention very quickly. Researchers believe the otherwise unprecedented speed in the changes may be because a TBI is a one-time, external injury rather than progressive disorder. The participants noted improvements in gait quality, increased ability to multitask such as walking and looking, and improved balance, and reduced pain, among other improvements. After the initial study, one participant's device broke, causing a circumstantial withdrawal phase. Researchers noted a decrease in function almost back to her baseline that was evident within days (TCNL, personal communication, 2012).

CN-NINM Theory

The CN-NINM intervention was initially discovered as a result of numerous observations of functional improvements while using oral electrical stimulation for other purposes such as sensory substitution. However, the neurological basis of how the intervention works is not yet thoroughly understood. Studies that have examined the effects of CN-NINM have been of case study format and focus primarily on observing functional changes in participants. These small studies have included several diagnostic categories to determine which types of individuals may receive the most benefit. No published research has been completed to understand the biological or neurological changes. The two fMRI case studies previously mentioned again provide some general conceptual support, but are not conclusive.

CN-NINM investigators believe that the large amounts of constant stimulation to the brain from the PoNS™ device floods the brain and primes it for learning. The priming effect makes the training activities particularly important to maximize the learning of intended tasks. In the fMRI case studies, the stimulation particularly appeared to affect the brainstem and cerebellum as the cranial nerves conducting the stimulation lead directly into the brainstem. Moreover, this form of nervous system stimulation uses naturally existing neural pathways as opposed to providing external stimulation to large areas of tissue (such as in TMS). The sensory input travels along the internal cranial nerves so is exactly targeted as input to the brain through normal nerve physiology. This contrasts the more artificially injected stimulation provided directly to the brain without normal

nerve and brainstem mediation. Affected centers appear to be those responsible for movement coordination and sensory integration which is likely a component of why balance and gait improvements have been noted in many participants.

As the stimulation follows normal pathways, it also may influence the rest of the brain through its network of normal interconnections both synaptic and extrasynaptic circuitries (again with the stimulation from “the inside out”, not “outside in”). Because of the extensive amount of stimulation and the brain’s neuroplasticity, the information processing and connections for functional tasks increase in efficiency and effectiveness (personal communication, TCNL, 2012-13, unpublished manuscripts, 2013). Additional research is required to fully understand the neurological changes related to the CN-NINM intervention.

Traumatic Brain Injuries

Individuals with TBIs often experience permanent gait impairments. Gait abnormalities common after TBIs, changes in step lengths and stance times on affected limbs and slow gait, may contribute to an increased risks of falls and reinjury as well as limited community access (Williams, Morris, Schache, & McCrory, 2009). In addition to gait changes, many individuals note increased impulsivity, decreased problem solving, and reduced ability to multitask (McCulloch, Buxton, Hackney, & Lowers, 2010). These impairments amplify the physical limitations and would be expected to further increase the risk of reinjury.

The lasting impairments are particularly significant when considering the scope and cost of TBIs. At least 1.7 million people are affected by a TBI in the United States each year (CDC, 2010). A 2000 CDC report estimated the total

cost of mild TBIs was \$12 billion; each person with a severe TBI costs between \$600,000 and \$1,870,000 in his or her lifetime (CDC, N.D.; Rezai & Corrigan, N.D.). Traumatic brain injuries are a large scale, expensive problem causing permanent disabilities or reductions in function. Currently rehabilitation does not have a practical, effective solution for addressing most lasting TBI effects.

The study described in this paper used participants with TBIs to determine if quick effects and withdrawal effects of CN-NINM could be detected. This paper describes the first study to systematically document a withdrawal phase.

Research Questions

The research team was interested in several aspects of the CN-NINM intervention. This research is exploratory and attempts to observe effects and side effects of CN-NINM and to observe and measure changes it may produce or augment in a person with a TBI. Since withdrawal effects from the CN-NINM intervention are potentially possible, this study chose to include a formal withdrawal phase. Research questions included asking how long it would take to see results, how long the results would last, and how long any improvements would last after ceasing the intervention. The research team developed four hypotheses: 1) Participants' functional gait quality will increase during each intervention week. 2) Participants' confidence with gait tasks will increase during each intervention week. 3) Participants' functional gait quality will decrease during each withdrawal week. 4) Participants' confidence with gait tasks will decrease slightly during each withdrawal week.

Methods

Research Design and Participant

This single case study implemented a classical A-B-A-B-A experimental design with five day phases, Monday-Friday. The participant, referred to as DS, was an individual with a TBI 27 years prior secondary to a motor vehicle accident that resulted in a severe TBI requiring approximately a year of rehabilitation training, and multiple, lasting orthopedic injuries. Because of these injuries, DS used a left Ankle Foot Orthosis (AFO), had a flat, metal plate for support in his right shoe, and had a cane he could use if he felt unstable or was walking long distances. DS works full-time in the community.

For the past 21 years, DS has been going to a local fitness center each weekday morning to stretch his heel cords and routinely exercise his upper body. He reported avoiding substantial physical activity involving balance or his lower extremities because that type of increased activity caused pain in his lower extremity and lower back and increased spasticity. He reported he has avoided using treadmills since 1992 as he did not feel safe using them. DS had been receiving Botox injections in his left lower extremity for two and a half years prior to the study to reduce pain, tone and improve the fit of his AFO.

Inclusion and Exclusion Criteria

DS lived in the community, was not receiving any rehabilitation services, and self-identified as having a balance and gait impairment caused by his brain injury. He did not use tobacco products. DS did not have a contagious mouth disease, an electrical device/implant such as a pacemaker, nor a major change

in medication type or dosage within three months of enrollment. Participants had to be very motivated, as the study used an intensive, five-week protocol which required significant time and physical and mental effort.

Instrumentation

Seven standardized measures were used during this study. Two balance/gait assessments were used in their entirety, components of two functional gait assessments were used, and three self-report assessments. Two self-report assessments, the Community Integration Questionnaire and Participation Objective, Participation Subjective, were collected to evaluate changes over a longitudinal study and will not be discussed in this paper. The remaining assessments are listed in the order completed.

Timed Up and Go

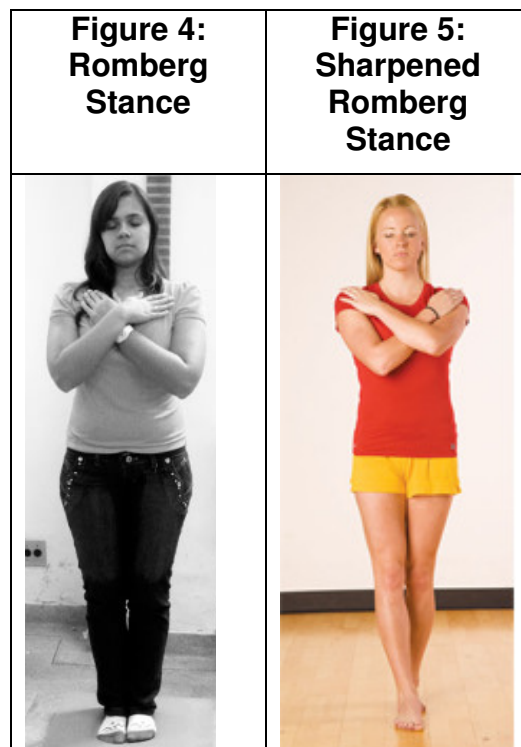
The Timed Up and Go (TUG) assesses a participant's speed rising from a chair, walking 3 meters, turning, returning to the chair and sitting (Podsiadlo & Richardson, 1991). The primary researcher recorded the time to complete the task; qualitative information was not used. Shorter times indicate better performance. A study of community dwelling adults found cut-off scores to be times below 13.5 seconds for risk of falls (Shumway-Cook, Brauer, & Woollacott, 2000). The Timed Up and Go has not been extensively tested for populations with TBIs. However, a study of children with TBI found excellent test retest reliability (ICC= .86) (Katz-Leurer, Rotem, Lewitus, Keren, & Meyer, 2008).

Romberg and Sharpened Romberg Test

The Romberg and Sharpened

Romberg tests assessed the participant's balance with and without vision.

Participants complete the Romberg with their feet together (see Figure 4) and Sharpened Romberg (see Figure 5) in a tandem stance. The participant has up to three trials to stand for a maximum of 60 seconds in each condition; longer times indicate better performance (Callegari, 2009). The Romberg and Sharpened Romberg have not been normed for TBI.



Minimal detectable change scores with a confidence interval of 95% for the Sharpened Romberg with eyes closed ranged from 3-9 seconds and with eyes open ranged from 9-10 seconds. Test retest reliability values (ICC) for volunteers aged 55-75 years old were 0.72 and 0.76 for eyes closed and 0.90 with eyes open (Steffen & Seney, 2008).

Dynamic Gait Index

The DGI assesses functional gait tasks on a 4 point scale (0-3). Higher scores indicate better performance. Four components from the DGI were used for this study. The tasks were: 1) Gait with horizontal head turns, 2) Gait with vertical head turns, 3) Step over an obstacle (See Figure 6), and 4) Step around

obstacles. Normative data for people in the same age bracket as DS includes a mean score of 23.9 with a range of 22-24 and a standard deviation of 0.4 (Vereeck, Wuyts, Truijen, & Heyning, 2008).

Community Balance and Mobility

Scale

The Community Balance and Mobility (CB&M) Scale was created for high functioning, community dwelling patients after a TBI to assess lasting effects in functional gait and balance tasks using a 6 point scale (0-5). Higher scores indicate better performance. The minimal detectable change, determined by using a 90% confidence interval, was 8 points (Howe, Inness, & Wright, 2011). Overall the CB&M Scale has high reliability for intra-, inter- and test-retest reliability with intraclass correlation coefficients of 0.977, 0.977, and 0.898-0.975 (for immediate and 5 days later test-retest), respectively. A Cronbach's alpha for internal consistency was 0.96 and 0.95, indicating a high correlation among items. All but one task met a priori inclusion criteria for content validity when scored by a focus group of physical therapists. (Howe, Inness, Venturini, Williams, & Verrier, 2006). Importantly, it correlates well with community integration scores (Howe & Inness, 2011).

Figure 6: Participant completing the DGI task "Step over an Obstacle"



This study completed the following 5 of 13 tasks: 1) Unilateral Stance (on right and left foot, timed), 2) Tandem Walking, 3) Crouch and Walk (timed), 4) Forward to Backward Walking (timed), 5) Step ups onto a single stair (beginning with right foot and left foot, timed; see Figure 7). The reliability and validity scores described are for the assessment completed in its entirety and may not be accurate for the components used in this study. The entire assessment was not completed as several tasks caused the participant pain; this is described in detail in the Procedure section below.

Figure 7: Participant completing CB&M Scale task “Step- Ups”



Modified Gait Efficacy Scale

The Gait Efficacy Scale assesses self-reported confidence completing common daily activities. A 2011 modified Gait Efficacy Scale (mGES) added tasks commonly experienced in daily activities. The mGES has a test retest reliability ICC of .93 (CI 0.85-0.97) after one month with a Cronbach's alpha of 0.94 (Newell, VanSwearingen, Hile, & Brach, 2012). The 10 item scale uses a 10 point Likert-like rating scale (1-10). Higher scores indicate more confidence with the task; a change of 6 points indicates a “true” change in confidence (Newell et al., 2012). The mGES was not normed for participants with TBIs and the assessment was modified further for the current study (GES-m) to include two

additional tasks that may be difficult for individuals with a TBI. The tasks assess confidence walking in a crowd and walking down aisles. (See Appendix B for the GES-m.)

Procedure

This study based its protocol on similar protocols established at TCNL where the primary researcher received training. The protocol was an intensive, five-week protocol with daily visits and twice daily visits during intervention weeks. After receiving approval through the University of Wisconsin Milwaukee's Institutional Review Board, participants were recruited primarily at local TBI support groups. Three participants completed a phone screening. One participant (DS) was eligible for and completed the study. Prior to beginning data collection, DS met with the primary researcher to review and sign the informed consent. DS then completed the POPS, CIQ, GES-m, and CB&M Scale. Per the protocol, the data from this day would be thrown out and the day was intended to familiarize DS with the assessments to eliminate a one time learning effect due to comfort with the assessments and anticipation of questions.

During the completion of seven components of the CB&M Scale, DS experienced pain in his lower back and left lower extremity that persisted approximately 48 hours. The pain appeared to be musculoskeletal and caused by his orthopedic injuries and avoidance of these tasks for the previous 20 years. After further discussion, he expressed interest in continuing the study with the tasks that did not cause pain, thus the addition of the TUG, Romberg, Sharpened Romberg, and tasks from the DGI. These tasks were chosen to assess similar

constructs as the CB&M Scale in a graded manner to eliminate the pain experienced.

Weeks 1, 3, & 5: Baseline and Withdrawal Weeks

During non-intervention weeks, DS completed the balance and gait tasks each afternoon (Monday-Friday) and the self-report scales on Friday afternoon after the gait tasks. He returned the PoNS™ device during withdrawal weeks, and was encouraged to try to maintain his same routine as prior to the study, not continuing to complete the training activities he learned. The researcher encouraged DS to complete subjective, unstructured journaling throughout the study regarding his experiences, any changes he noted, and what he attributed the changes to. Each day the participant and researcher discussed any changes or questions he had. These activities remained consistent during intervention weeks as well.

Weeks 2 and 4: Intervention

During intervention weeks, DS completed two Intervention Sessions, one in the morning and one in the afternoon. The afternoon session was completed after finishing the same tasks as the baseline week. Each Intervention Session included three CN-NINM sessions; each CN-NINM session includes a 20-minute personalized Targeted Training Activity Session and concurrent use of the PoNS™ device. The CN-NINM sessions consisted of balance, relaxation, and gait training sessions. Balance trainings consisted of static standing on foam balance pads or sitting on a yoga ball with eyes closed. Relaxation trainings, completed between the other sessions, did not use the PoNS™ device. The

sessions focused on body and breathing awareness during quiet sitting to reduce distractibility and improve focus and attention to task. DS initially completed gait training sessions on a treadmill, expanding to over-ground walking to integrate skills mastered on the treadmill. Gait tasks included maintaining upright posture in the middle of the treadmill, reducing instances of toe drag, initiating reciprocal arm swing, taking even step lengths etc...

On the first day of Week 2, the participant was provided with a PoNS™ device and educated on the use and care of the device. He explored the device and discussed questions with the researcher until he expressed a high comfort level with the device, stimulation, and maintenance.

DS completed two additional CN-NINM sessions at home each day. These sessions involved similar activities as what was practiced during the day but with less intensity to ensure participant safety. Example sessions included using the PoNS™ when stretching his left heel cord and walking over ground as well as while completing standing balance tasks at the kitchen sink.

Subjective Reports

During each Intervention Session, the primary researcher documented observations and changes noted and reported. During withdrawal weeks, the primary researcher documented observations and changes once each day. Self-reported changes were obtained from the ten single spaced typed notes pages and are included if they were reported more than once.

Data Analyses

All assessments were videotaped for later analysis. The primary researcher recorded times for the time-based assessments. Data were graphed using Excel. Comparisons across phases were evaluated and analyzed using a combination of visual and statistical methods. Visual analyses included trend, level, variability, and immediacy of effect. Statistical analyses used percentages of data overlap including percentage of non-overlapping data (PND), percentage exceeding the mean (PEAv) and median (PEM), and pairwise data overlap (PDO).

Results

Results are described in terms of: 1) timed scores, 2) data rated by trained assessors, 3) self-report scale responses, and 4) self-reported changes.

One of the study's hypotheses was that there would be a difference in functional gait between intervention and withdrawal weeks. This was not consistently supported by any of the measures. A second hypothesis indicated that gait confidence would also change during intervention and withdrawal weeks. Several of the participant's confidence scores support this hypothesis.

To analyze results, 35 graphs were created and analyzed (see Appendix C). Each graph was analyzed within and across adjacent and like phases. 16 graphs visually supported the hypotheses at least mildly. However, most of these provided mild support of the hypotheses; some lightly trended toward expected results. It is not clear that the changes are stably greater than minimal detectable change values for the measures applied. The graphs depicted in this section are representative samples from the full set of graphs to highlight results.

1) Timed Scores

Timed scores included the Timed Up and Go, Romberg, and Sharpened Romberg, not the timed components of the CB&M Scale.

Timed Up and Go Scores

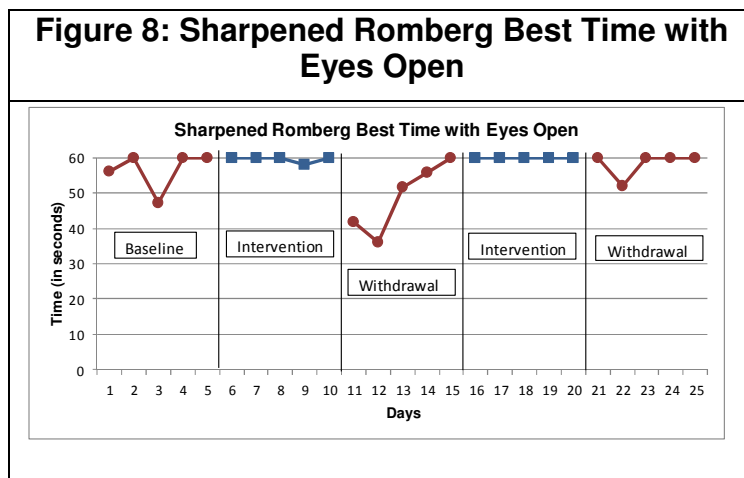
Each trial time was below the 13.5 seconds cut-off time for fall risk in community dwelling adults (Shumway-Cook et al., 2000) indicating DS was a low fall risk according to the Timed Up and Go. DS's scores remained fairly stable, with a slight trend toward decreasing times across the study. The only phases

with significantly different times was between the baseline and first intervention phase, with 96% of data being outside the PDO and 100% of data points being different than the PEM and PEAv.

Romberg and Sharpened Romberg Scores

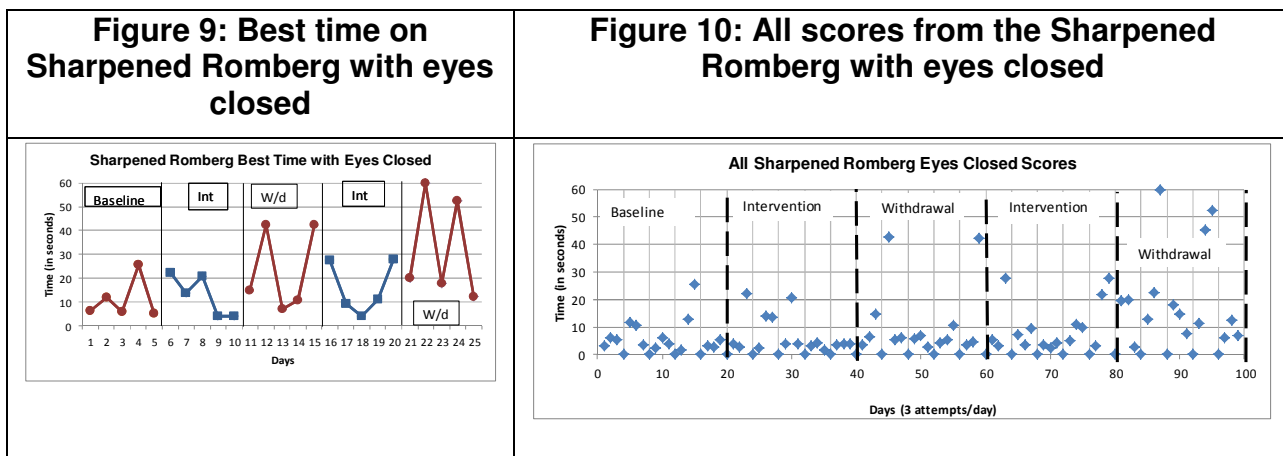
The participant reached 60 seconds, the maximum time for the Romberg Test, on each trial during each phase both with eyes open and eyes closed. Since no change was evident, the Romberg will not be discussed further.

Traditionally, Romberg and Sharpened Romberg scores are evaluated using the best time from the three trials. Figure 8 shows the best time for the Sharpened Romberg scores with eyes open. Between both the first intervention and first withdrawal and the first withdrawal and second intervention there was 80% PDO. Between the first intervention and first withdrawal there was an 80% difference in the PEM, PEAv, and PND as well as a noticeable immediate decrease in level. Between the first withdrawal phase and second intervention phase there was 0% PND, but 100% PEM and PEAv.



Eyes closed Sharpened Romberg scores were evaluated three ways due to each phase's increased variability when using the best time scores. Graphs were: 1) best time (see Figure 9), 2) average time, and 3) all raw data points (see

Figure 10). The most notable changes in scores occurred between the baseline and first intervention phase with 60% PEM and PEAv. The final three phases show a substantial amount of variability in scores in each phase.



2) Data rated by trained assessors

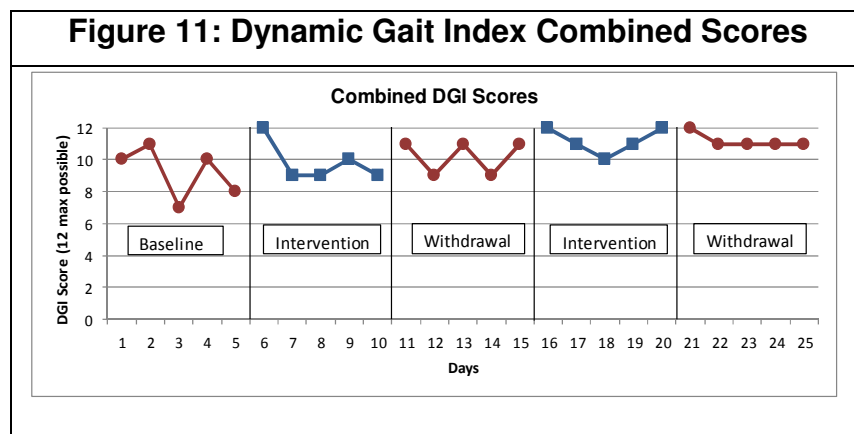
Two raters were trained together on the DGI and CB&M Scale. Rater 1 was unfamiliar with the study design and scored all data from the participant; Rater 2 scored 40% of the data (10 out of 25 days). Both used randomly ordered videotapes when scoring the data. Inter-rater reliability was analyzed using SPSS (SPSS Version 19). Data was ran as a two way random test. The Intraclass Correlation Coefficient (ICC) for the average measures of the DGI was .731 (which matched the Cronbach's Alpha). The ICC for the average measures of the CB&M Scale was .798 (which also matched the Cronbach's Alpha).

Each task of the assessments was graphed separately based on the scores provided by Rater 1. The total score was then determined for both the DGI and CB&M Scale by adding the component scores for each day.

Dynamic Gait Index Scores

Total DGI scores data display a slight increasing trend across each phase (see Figure 11); no decrease in scores was noted during withdrawal weeks.

No significant differences were found between any of the phases. Graphs of three of the four DGI tasks looked similar to the



combined scores (the fourth showed no change due to a ceiling effect). Graphs of individual tasks showed variability similar to the combined scores.

Community Balance & Mobility Scale Scores

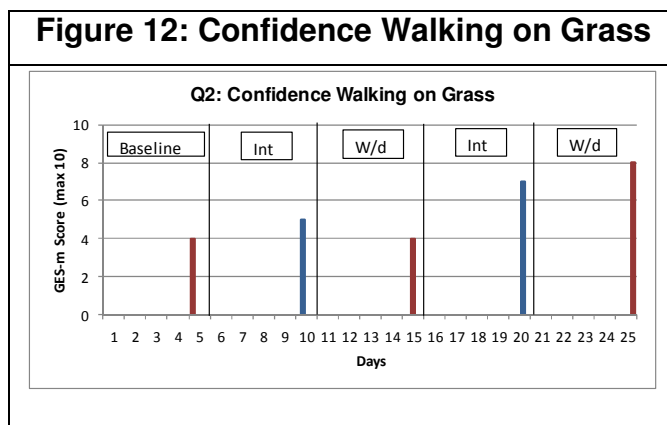
The total CB&M Scale scores display a stable/slightly increasing trend across phases. No decrease in scores is noted during withdrawal weeks. Substantial differences were noted between the baseline and first intervention week, with 100% PEM and PEAv, and 80% PDO. However, because the baseline trend is steadily increasing and there is not a change in the intervention week level, these differences may not indicate a change in function.

Four of the seven CB&M Scale task graphs showed similar trends as the combined score graphs. Three of the component tasks showed no change over the study. Unilateral stance while standing on his left foot showed a floor effect, only scoring one point out of five on two days of the study. Step-ups onto and off

a single step also showed no change throughout the study, scoring a “3” each day except one when initiating with the right and left foot.

3) Modified Gait Efficacy Scale

Self-report scores were collected once per phase. Graphs were made for each question as well as the average score. Self-reported confidence in the final phase was not less than the first phase for any question. Typically, the individual graphs showed an increase in confidence during one or both intervention weeks, some decrease in confidence during the first withdrawal week, and either stable or increasing confidence during the final withdrawal week (see Figure 12). Two graphs did not fit this pattern, including confidence going down stairs not holding onto a railing and confidence walking long distances. On each of these, confidence decreased during intervention weeks; however, confidence by the end of the study equaled or was greater than initial confidence.



4) Self-Reported Observations

Throughout the study, DS remarked through journaling and to the primary researcher on several changes he attributed to the intervention that were not measured by assessments during the study. Key observations are listed below.

- A **reduction in tone** of his left lower extremity allowing his AFO to fit more securely. This was noted to the researcher on the afternoon visit of the first day of the intervention and often repeated during both intervention weeks.
- An **increased tolerance for exercise without** negative consequences such as **pain or unsafe movements**. Although DS was initially skeptical of his ability to complete 20 minutes of gait training on a treadmill, he began remarking by the middle of the first intervention week that he felt very good after the treadmill activities and wanted to keep walking.
- An **increase in confidence in his walking abilities**. Because his AFO fit better, DS felt more confident in the AFO supporting his foot and therefore his walking ability. He noted he had better toe clearance and tripped less during the day. DS also noted at the end of the first intervention week and several times during the second intervention week that his walking had not felt so “good” since his injury. He indicated being interested in going for long walks and being more physically active because of this new positive feeling he experienced when walking during and after the gait training sessions.
- A **reduction in and elimination of pain**. DS indicated when he “overdoes” physical activity, he experiences pain in his left lower extremity, particularly in his foot. By the middle of the first intervention week, he indicated he was not experiencing pain with increased physical activity. By the end of the second week of intervention, he had a reduction in overall pain, elimination of pain from activities that previously would have caused pain, and a significant reduction in pain duration when he did feel pain related to physical activity.

- In addition to balance and gait changes, DS also indicated that he **used his left arm/hand more frequently and with less feelings of awkwardness.**

Discussion

DS reported several changes over the course of the study, but they were not confirmed by the a priori chosen assessment measures. Nonetheless, the results are informative to researchers and clinicians planning future CN-NINM research or treatment. The primary researcher believes less change was evident during the videotaped assessments than normal walking; this difference may be attributed to the short duration of the assessment tasks and/or the attention and focus provided for the assessment tasks. Consistent across all phases, the participant's gait looked substantially different when walking to and from locations and while talking to the researcher than it did during the taped assessments.

Overall results on the assessment measures showed slight trends toward improvement on balance and gait tasks. Several factors could influence this finding. It is possible the intervention facilitated greater learning of the training tasks. Some improvement would be expected from the training even without the PoNS™ device. It was hypothesized that participant scores would decrease during the withdrawal. This was not the case. It is very possible that the new skills were learned and integrated during the intervention phases and therefore not able to be withdrawn. Although a learning effect is likely, the tasks used were chosen for their functional implications; tasks were common daily activities, like walking and looking vertically or horizontally, or picking an object up off the floor.

1) Timed Scores

The Timed Up and Go data were all within the accepted range for community dwelling adults, therefore, any differences noted are not as

meaningful. Sharpened Romberg with eyes closed scores showed a great deal of variability. Reasons for the variability may be related to DS's attention and focus on the task. He found it difficult to attend to tasks without becoming distracted. It is also possible his orthopedic injuries and compensation strategies may have influenced his scores. Much of the variability is not accounted for on this task.

2) Data rated by trained assessors

Neither the DGI nor CB&M Scale showed significant change in the DS's function during the study. One rater observed changes in DS's function that were not reflected in the scores due to the assessment criteria. For example, to pick up an object from the ground, DS typically stopped walking and went down onto his right knee. Several days he paused, lowered his knee, but did not touch his knee to the floor or use the floor to push himself up. However, because forward momentum was stopped, the days were scored the same. Similarly, during a forward to backward walking task, the rater noted DS usually took four steps to turn, securing a consistent test score, although the quality of the backward walking showed changes. These observations indicate the assessments may not have been sensitive enough or appropriate to detect the changes.

3) Self-Report Scale Responses

Scores on the GES-m followed trends similar to those hypothesized. The differences observed did not reach the level set to determine a true change in confidence. Decreases in confidence, particularly at the first withdrawal week may be due to DS's greater awareness of his gait deviations. DS remarked several times during the intervention weeks that he believed his gait to be

significantly better than it had been in years or possibly since the injury. During the first withdrawal week, the participant noted several negative aspects returning. When his gait felt worse, due to factors like the return of high tone, DS was more observant about his strategies to work around his limitations, such as hip-hiking to provide greater toe clearance rather than increasing hip and knee flexion. The increase or maintenance of confidence during the second withdrawal phase may be attributed to increased exposure to many of the GES-m tasks during gait trainings like walking outside on grass and walking long distances.

4) Self-Reported Observations

The self-reported observations include observations from the participant and primary researcher and are discussed separately below.

Participant Observations

DS attributed several changes to the CN-NINM intervention including a reduction in tone, which returned during the withdrawal weeks, a reduction in pain, which came back to a degree during the withdrawal weeks, and a more natural feeling gait, which returned to baseline during withdrawal weeks. During the first withdrawal week, DS indicated not being sure if he was functioning worse than he had prior to the study, or if he were simply more aware of his limitations and maladaptive behaviors. By the 3rd day of the intervention (out of ten total intervention days), DS remarked he considered the study a success.

Prior to the study, DS could participate in physical activity for limited amounts of time without developing pain in his left foot. While using the device,

he was able to complete 20 minutes of strenuous activity for the participant on the treadmill without having pain or feeling “tight” or poor after the activity.

Researcher Observations

Several observations about DS’s changes were made by the primary researcher. During initial treadmill gait trainings, DS needed maximum cueing to stay in the center of the treadmill. By the second day of the intervention, he required minimum cueing to stay in the center. Several tasks were mastered with similar speed, including reducing the number of times his left foot did not clear on the swing thru. This was addressed the first two days of the intervention, then integrated into remaining treadmill and over-ground walking with the researcher.

In addition to improvements during training sessions, the researcher noted a slight change in gait when walking within the testing site. Particularly during the second intervention week, DS appeared to integrate training tasks well. He took more even step lengths, occasionally integrated unconscious, slight left arm swing, and did not twist his body as greatly to walk leading with his right side.

On the first day before the protocol began, 7 out of 13 CB&M Scale tasks caused the participant significant, lasting pain. On the last day of the second intervention week, after the regular assessments, the researcher asked DS if he wanted to try the whole CB&M Scale. He agreed and was able to complete six of the seven tasks pain-free. The primary researcher noted that the tasks on the first day looked uncontrolled, unsafe, and impulsive. On the last intervention day, the tasks looked safe and more controlled. Although decrements in quality were still noted, the researcher did not have to stabilize DS during any of the tasks nor

was the researcher concerned for his safety. The only task he did not feel comfortable trying was running, which he attributes to his orthopedic injuries.

Monthly Follow-up

If participants experienced positive functional changes, researchers did not want to remove the PoNS™ device and potentially lose any functional gain. DS accepted the opportunity to participate in up to a three-year longitudinal study, with the option to drop out whenever he no longer wanted to use the PoNS™. The longitudinal study includes monthly contact (phone or email) and an in-person visit every 6 months to complete the assessments that were used throughout the study. In the meantime, DS uses the device independently and records the number of times each day he uses the device.

In the four months since the first study ended, DS made five key observations. 1) His tone continues to be reduced. He is able to achieve a quality stretch and his AFO continues to feel like it is fitting well. 2) His left hand continues to feel more natural to use, although it requires additional conscious thought, and he is crossing midline with his right hand less. 3) He is able to complete more physical activity with less pain. He has started to use the treadmill when exercising, increasing both speed and incline. He noted being overall pain free since using the PoNS™ device, and when he did experience pain, the pain had reduced duration. 4) DS mentioned several times during the study his interest in volunteering more. Since the study ended, he began three new volunteer opportunities and was maintaining two at last discussion. 5) Perhaps the largest indicator of change since the study is that the participant cancelled his

upcoming Botox injection for the left lower extremity. He indicated that his leg feels as good as it did before he began Botox injections. He indicated preferring an intervention that did not include injecting himself with chemicals.

Limitations

Four limitations to this study were identified. First, only one participant was eligible for and completed the study. Although the study provides valuable information regarding his experience, results and conclusions from this study are not generalizable to a larger population. Second, participant was not an ideal candidate because of his orthopedic injuries, presentation of symptoms and strong compensation strategies that may have limited progress. Compensation strategies included taking large left steps for greater heel strike, hip-hiking to achieve toe clearance, and putting his right knee on the ground to pick up an object from the floor. Participants with vestibular impairments may observe more significant benefit from the intervention, although more research is required.

Third, the primary researcher completed the intervention and data collection and neither the primary researcher or participant was blinded to the study. As subjective outcomes can be influenced without blinding, the primary researcher was cognizant of what she said and to follow established protocols. Another attempt to reduce bias was the use of randomized video assessments scored by reviewers unfamiliar with the study. Last, the measures selected, though sensitive to small changes, may not have been sensitive enough or appropriate to detect observed changes. However, the changes were reported and some of the measures showed trends similar to the observations noted.

Implications for Occupational Therapy

CN-NINM shows promise as a technology based rehabilitation intervention. The positive changes DS noted after the first intervention session had significant implications on his motivation to continue the protocols. With additional research, CN-NINM may facilitate greater gains in rehabilitation. Once trained, participants can use the CN-NINM intervention independently, which may allow patients to master skills more quickly and integrate more skills independently so each session with an occupational therapist can focus on learning new skills or integrating and mastering more complex skills.

In this study, DS noted a decrease in tone and pain. As both can be severe limitations to occupational therapy, reduction in both can be of great benefit for rehabilitation. Often a therapist must manage pain and tone prior to addressing other aspects of function. It is also becoming more popular to look for alternative treatment options to pharmaceuticals; the CN-NINM intervention provides an option for a non-invasive option that does not rely on medications.

Future Research

Future research could address several areas of study. Additional participants with TBI should be studied to determine the type of participants that may benefit most from the intervention. Future participants with TBI may include those with vestibular impairments and not those with tone. Studies should include longer phases to determine if phase lengths correlate to the intensity of changes. Studies should include a formal withdrawal period to determine any carry-over effects. Future studies may also test whether the device increases rapidity of

learning or level of performance. Last, additional research should study the effectiveness of home programs to reduce the time commitment for researchers and increase the feasibility of the study for participants.

Conclusions

Changes were observed in the participant's functioning, even though the assessment scores did not show a significant difference. Two changes were noted. First, DS indicated an almost immediate change in the tone of his left lower extremity, mentioning this change before the second intervention session on the first day. He indicated being pleased with the changes and that the intervention did not use medications. Second, DS reported decreased pain as well as reduced the duration of pain when pain was experienced.

The intervention was clearly acceptable to the client, preferred to pharmacologic interventions, and potentially practical because it does not require constant direct supervision, is not expensive, and appears to lack negative side effects. The CN-NINM intervention warrants additional research.

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PART III: APPENDICES

Appendix A: Supplemental PoNS™ Information

Supplement:

Investigation of Brain Plasticity in Response to Noninvasive Neuromodulation

I. Description of the Portable Neuromodulation Stimulator (PoNS)

The 'PoNSTM' system (ver. 2.0) has operational limits of 19 V (max) and 6 mA (nominally) on the tongue. The biphasic waveform is specifically designed to ensure zero net direct current to minimize the potential for tissue irritation. The system delivers triplets of pulses at 5 ms intervals (i.e. 200 Hz) every 20 ms (50 Hz) to a hexagonally patterned array of gold electroplated circular electrodes created by a photolithographic process used to make printed circuit boards. While the voltage and pulse timing to each electrode is programmed in the device and cannot be altered, the subject can adjust the pulse-width (0.4 - 60 μ s) by manipulating a pair of push buttons to directly control the stimulus intensity. At any instant in time, only one of the electrodes in each of the 16 sectors on the array is delivering stimulation. The remaining electrodes serve as the current return path to ground. Additionally, the stimulus intensity is mapped uniquely to each region of the tongue to insure that the perceived sensation is uniform across the entire array. This form of tongue stimulation has been used in our research for the last 13 years under multiple UW Health Sciences -IRB protocols for studies in balance, vision, and speech substitution (H2000-527, H2001-364, H2004-0375, H2000-0192, H2005-0222, H2007-0251), and for neuromodulation (H2008-0057, H2008-0252), with no adverse events [1-4].

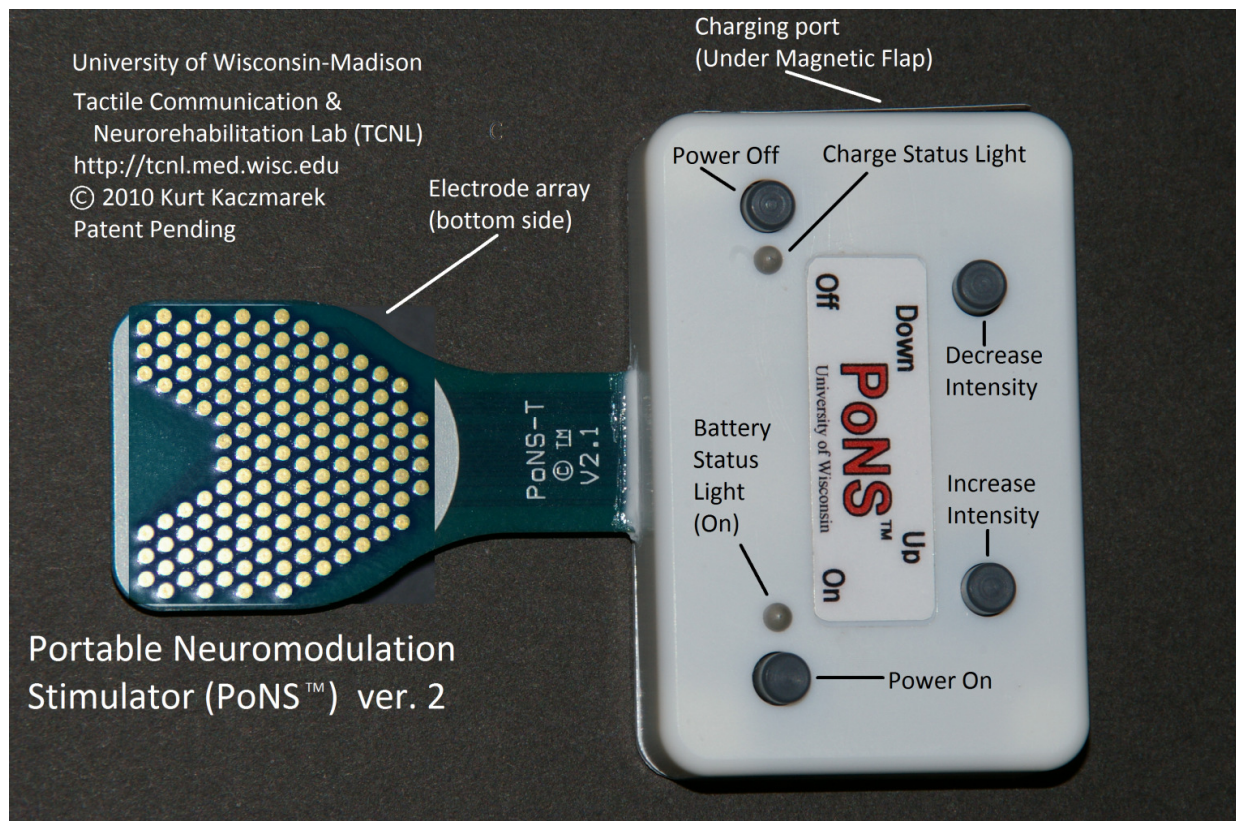


Figure 1. Image of the PoNS_v2.0 device.

Physically, the 32 mm wide by 0.84 mm thick oral tab is designed to fit into the upper cavity of the mouth, and contains the tongue stimulation array of 143 electrodes (1.50 mm diam., on 2.34 mm centers). The case of the T-shaped PoNS device measures 68 mm wide x 45 mm long x 15 mm thick, with a total mass of 56 gm¹. The user has complete control of the device, which has waterproof case, power and intensity control buttons, and status indicator lights (see Figure 1).

The PoNS fabrication is based on Class-II medical device design principles. It is powered by a rechargeable lithium-ion battery with built-in current-protection circuitry. Both the charging circuitry and the power connector are specifically designed to prevent device use while it is being charged, thereby preventing the possibility of electrical shock. An FDA approved USP Class VI biocompatible polymer is used to encapsulate the tab (excluding the electrodes) prevent saliva from harming the electronics. Array cleaning is accomplished with commercially available isopropyl alcohol.

II. Device Operation.

Procedurally, for each CN-NINM training session, subjects place the end of the tab containing the electrode array approximately 45 mm into the mouth so that it contacts the superior anterior surface of the tongue. The tab is held lightly in place by the lips and teeth. During CN-NINM training the recommended stimulation intensity, S_e , for each subject is defined as: $S_e = S_s + k[S_m - S_s]$, where S_s and S_m are the minimum threshold and maximum-comfortable sensation levels, respectively, and $k = 0.3 - 0.7$, i.e. the recommended intensity level is between 30% and 70% of the usable sensation range. If at any time the subject wants to stop the stimulation they may press the "Down" intensity control, press the "Off" button, or simply remove the device from their mouth.

Controls and features

- Power: "On" and "Off" pushbuttons. The device will remain on until "Off" is pressed or the battery is exhausted. The device will automatically shutoff when plugged into the charger.
- Intensity: "Up" button increases intensity, "Down" button decreases intensity. The buttons can either be used by individual presses, or held down to adjust intensity levels. To achieve the maximum intensity 63 individual presses are required, or the button can be held down for 8 seconds. Note: When the device turns on, it automatically starts at the lowest possible intensity, and the step sizes increase uniquely. The user may not experience desired stimulation levels until they reach the upper end of the intensity spectrum.
- Charge indicators: The lights surrounding the OFF button indicate charge status. Red means charging, green means charge is complete. The device can be used before charge is complete, but with reduced operating time.
- Operating indicators: The lights surrounding the ON button indicate battery status during operation. Green means normal operation. Yellow indicates the battery is low, but the device is still operating within specifications. When the battery charge is too low the device will turn off automatically.
- Charger jack: Connect only the supplied charger to this jack. Use of any other charger may damage the device or the charger. When charging, the red charge light will turn on. When fully charged the green charge complete light will come on. For safety, the device cannot be used while charging.

¹ The PoNS is designed and developed in the Tactile Communication and NeuroRehabilitation Laboratory (TCNL). The PC board and electrodes are fabricated by Advance Circuits (Aurora, CO), and surface-mounted IC components assembled by Prairie Digital (Sauk City, WI). Final inspection, verification and encapsulation performed at the TCNL by the investigators.

III. Rationale for designation as a non-significant risk (NSR) device.

A predicate technology, the commercially available BrainPort Balance device (Wicab, Inc), and developed by the investigators, received the NSR designation in 2006.

The PoNS device uses the same electrotactile waveform as the predicate BrainPort. It can also be considered non-significant risk device because, under 21 CFR 812.3(m), (summarized in [5]), a significant risk (SR) device is defined as one that:

- (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (2) is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health;
- (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Given the technical and functional considerations identified above, the PoNS can be considered a non-significant risk (NSR) device because it:

- (1) is *not* an implant device: the recommended use is only for periodic non-invasive placement on the tongue that is controlled by the user;
- (2) will *not* be used to support or sustain human life: the recommended use is for periodic application twice or three times each day for approximately 45 minutes each;
- (3) will *not* be used for substantial importance in diagnosing, curing, mitigating, or treating disease; only to address *symptoms* of neurologic disorders affecting movement control;
- (4) is intentionally designed to *not* present a potential for serious risk to the health, safety or welfare of a subject.

IV. References

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- [5] "Information Sheet Guidance For IRB's, Clinical Investigators, and Sponsors: Significant Risk and Non-Significant Risk Medical Device Studies." U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health (CDRH), January 2006.



AUG 12 2005

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. John Comerford
Vice President, General Counsel and Secretary
Wicab, Inc.
8476 Greenway Boulevard
Middleton, WI 53562

Re: I040581
Electrotactile signal stimulation of the tongue to treat patients with Bilateral Vestibular Dysfunction ("BVD").

Dear Mr. Comerford:

The Food and Drug Administration (FDA) has reviewed your PIDE submission, dated December 23, 2004, proposing a study using your Brainport™ Balance Device to treat in patients with Bilateral Vestibular Dysfunction ("BVD").

FDA has determined that your proposed clinical investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812, available on the internet at

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=812>).

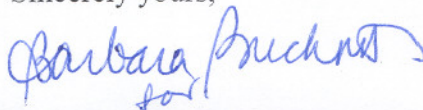
An IDE application is not required to be submitted to, or approved by, FDA for a NSR study. A NSR study is, however, subject to the abbreviated requirements described in § 812.2(b) of the IDE regulation. The abbreviated requirements stipulate that the sponsor of the investigation must label the device in accordance with § 812.5; obtain institutional review board approval of the investigation as a NSR study; ensure that each investigator obtains informed consent from each subject under the investigator's care; comply with the monitoring requirements of § 812.46; maintain records required under § 812.140(b)(4) and (5) and file the reports required under § 812.150(b)(1) through (3) and (5) through (10); and ensure that participating investigators maintain the records required by § 812.140(a)(3)(i) and file the reports required under § 812.150(a)(1), (2), (5) and (7).

Under the abbreviated IDE requirements, a sponsor must also comply with the prohibitions against promotion and other practices as identified in § 812.7. According to this section of the regulation, the sponsor of a NSR study, investigator, or any person acting for or on behalf of the sponsor or investigator is prohibited from promoting or test marketing the investigational device until after FDA has approved the device for commercial distribution; commercializing the device by charging a price greater than that necessary to recover the cost of manufacture, research, development, and handling; unduly prolonging the investigation; and representing the investigational device as being safe or effective for the purposes for which it is being investigated.

Page 2 - Mr. John Comerford

If you have any questions regarding our NSR determination or the abbreviated IDE requirements, please contact Mr. Neil R.P. Ogden at (301) 594-1307.

Sincerely yours,

A handwritten signature in blue ink that reads "Barbara Pruchno" with a small "for" written below it.

Mark N. Melkerson
Acting Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Appendix B: modified Gait Efficacy Scale (GES-m)

Modified Gait Efficacy Scale

Please answer the following questions regarding your confidence completing the following activities **WITHOUT** an assistive device (without a cane, walker, or wheelchair).

1. How much confidence do you have that you would be able to safely walk on a level surface such as a hardwood floor?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

2. How much confidence do you have that you would be able to safely walk on grass?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

3. How much confidence do you have that you would be able to safely walk over an obstacle in your path?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

4. How much confidence do you have that you would be able to safely step down from a curb?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

5. How much confidence do you have that you would be able to safely step up onto a curb?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

6. How much confidence do you have that you would be able to safely walk up stairs if you are NOT holding on to a railing?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

7. How much confidence do you have that you would be able to safely walk down stairs if you are NOT holding on to a railing?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

8. How much confidence do you have that you would be able to safely walk in a large crowd?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

9. How much confidence do you have that you would be able to safely walk down aisles in a store such as a grocery store?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

10. How much confidence do you have that you would be able to safely walk a long distance such as $\frac{1}{2}$ mile?

1	2	3	4	5	6	7	8	9	10

No Confidence

Complete Confidence

Appendix C: Data Graphs and Analyses

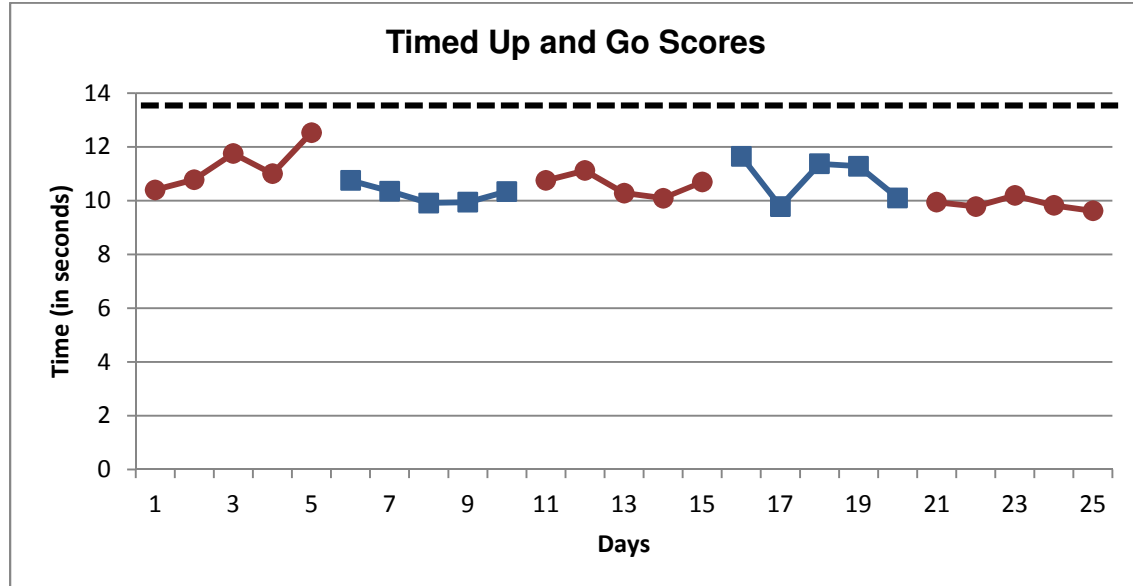
Protocol Used for Data Presentation

The following section presents the graphs and analyses for the data collected during this study. Graphs that are used in the research manuscript are designated with an asterisk (*). Each graph is assessed in the same manner.

Prior to collecting data, proposed analysis techniques to look at the data included visual analyses, basic trend lines using split middle celeration lines, percentage data overlap techniques, and two standard deviation band method analyses. Visual analysis methods included examining level, trend, variability, immediacy of effect, overlap, and consistency across similar phases. On the analyses below, consistency is included in Phase 4, comparing Phase 2 and 4, and in Phase 3 comparing Phase 1 and 3, and in Phase 5 comparing Phase 3 to 5. Four percentage data overlap techniques were utilized: percentage non-overlapping data, percentage exceeding the median, percentage exceeding the mean, and pairwise data overlap. Each of these techniques evaluate the data based on the trends expected from the hypotheses. For example, for percentage non-overlapping data, the highest score is used for baseline and withdrawal phases and counts only data points higher in the intervention. The lowest score is used for intervention phases and counts include only lower points in the withdrawal weeks. These follow the hypotheses that the participant would have better scores during intervention weeks and worse scores during the baseline and withdrawal phases.

After graphing the data, two observations altered the analyses completed. First, several tasks and assessments had high variability and few phases stabilized. This often made basic trend lines misleading and uninformative. Because the trend lines were not deemed to be accurate or representative, there were not used for the data collected and are not shown below. Subsequent studies may considered lengthening each phase to provide a more accurate celeration line. A second observation made was that the each phase scores were relatively consistent, that is, there were no noticeable level differences in data. This makes the use of the two standard deviation band method unnecessary, as no change was noted that would be close to showing significance with this method. Therefore, the two standard deviation band method was not completed for the data and is not included below.

Timed Up and Go



The black dashed line represents the cut-off scores for community dwelling adults for risk of falls (13.5 seconds). All data points for the participant fall below this, indicating he is at low risk for falls according to this assessment.

Phase 1: Baseline

Level: Low/Medium

Trend: Increasing

Variability: Stable

Phase 2: Intervention

Level: Low

Trend: Decreasing very slightly

Variability: Stable

Immediacy of effect: N/A

Data overlap (phase 1 to 2):

PND: 0%

PEM: 100%

PEAv: 100%

PDO: (4+5+5+5+5/25) 96%

Phase 3: Withdrawal

Level: Low

Trend: N/A

Variability: Low/medium

Immediacy of effect: N/A

Data overlap (phase 2 to 3):

PND: 20%

PEM: 60%

PEAv: 80%

PDO: (1+3+5+5+3/25) 68%

Consistency: Low

Phase 4: Intervention

Level: Low/Medium

Trend: N/A due to variability

Variability: Medium

Immediacy of effect: N/A

Data overlap (phase 3 to 4):

PND: 20%

PEM: 40%

PEAv: 40%

PDO: (2+2+2+1+2/25) 36%

Consistency: None

Phase 5: Withdrawal

Level: Low

Trend: Stable/slightly decreasing

Variability: Low

Immediacy of effect: N/A

Data overlap (phase 4 to 5):

PND: 0%

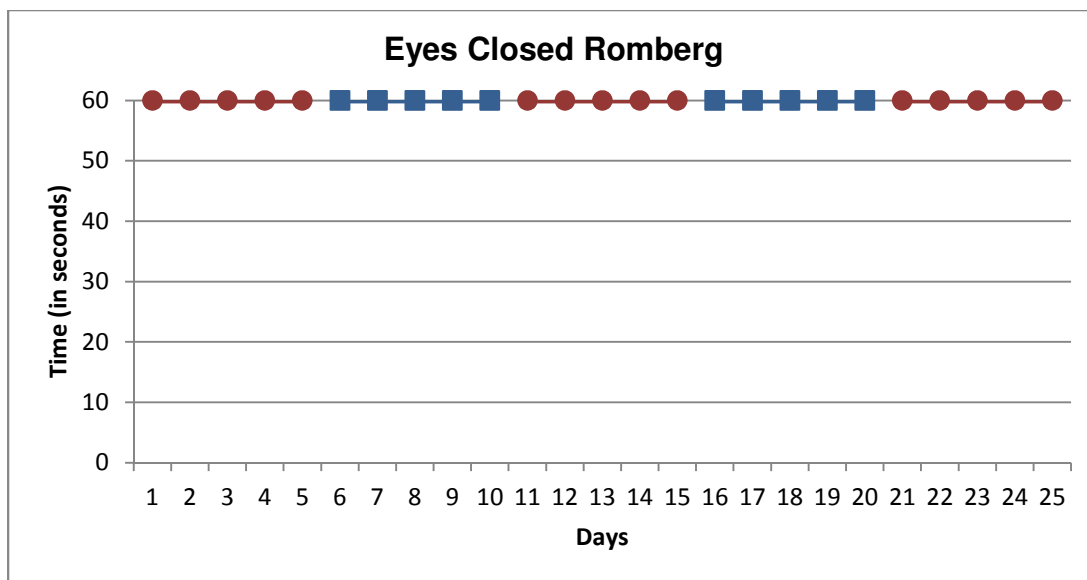
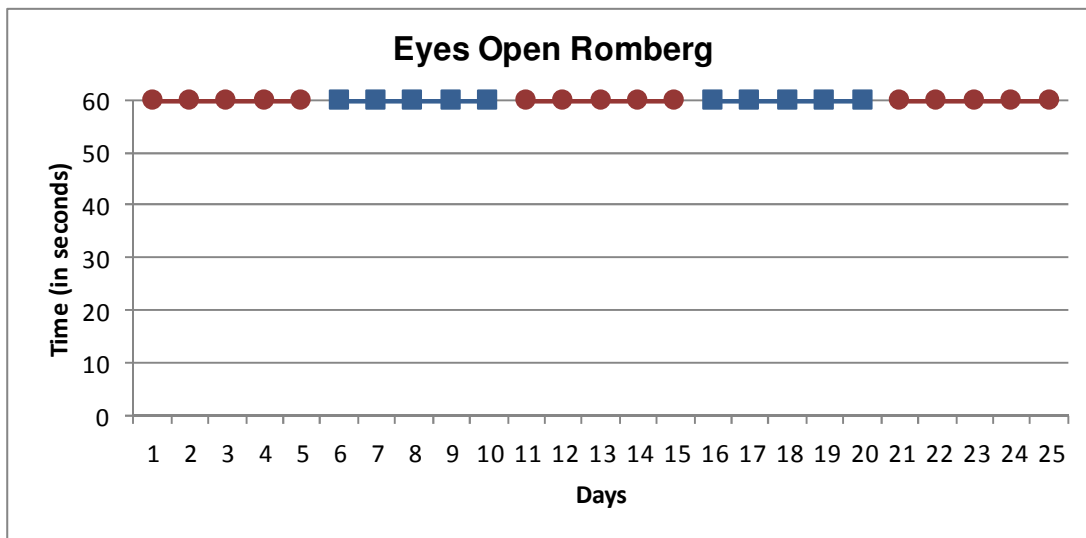
PEM: 0%

PEAv: 0%

PDO: (0+3+0+0+1/25) 16%

Consistency: Moderate

Romberg



Phase 1

Level: Stable

Trend: Stable

Variability: None

All Subsequent Phases

Level: Stable

Trend: Stable

Variability: None

Immediacy of effect: None

Data overlap: 0%

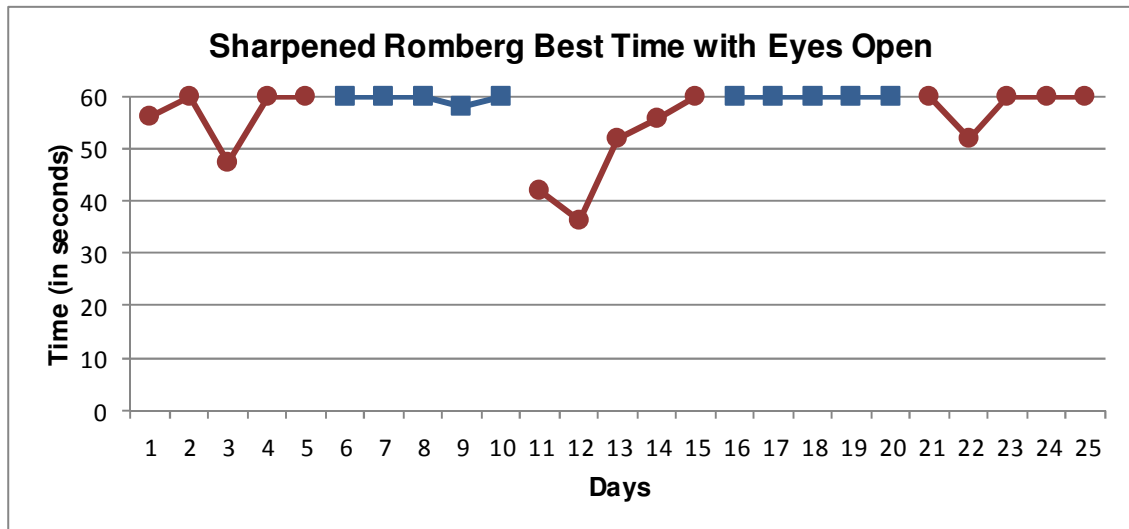
Consistency across phases:

Complete consistency

Additional Analyses

No changes were noted in ability due to a strong (complete) ceiling effect at each session. Therefore, no additional analyses were deemed appropriate.

*Eyes Open Sharpened Romberg



Phase 1

Level: High
Trend: Relatively stable
Variability: Low

Phase 2

Level: High
Trend: Stable
Variability: Very little
Immediacy of effect: N/A (ceiling effect)
Data overlap (phase 1 to 2):
PND: 0%
PEM: 0%
PEAv: 100%
PDO: (5+0+5+0+0/25) 40%

Phase 3

Level: Medium to high
Trend: stable, increasing
Variability: Slight
Immediacy of effect: Immediate notable decrease
Data overlap (phase 2 to 3):
PND: 80%
PEM: 80%
PEAv: 80%
PDO: (4+4+4+4+4/25) 80%
Consistency: None

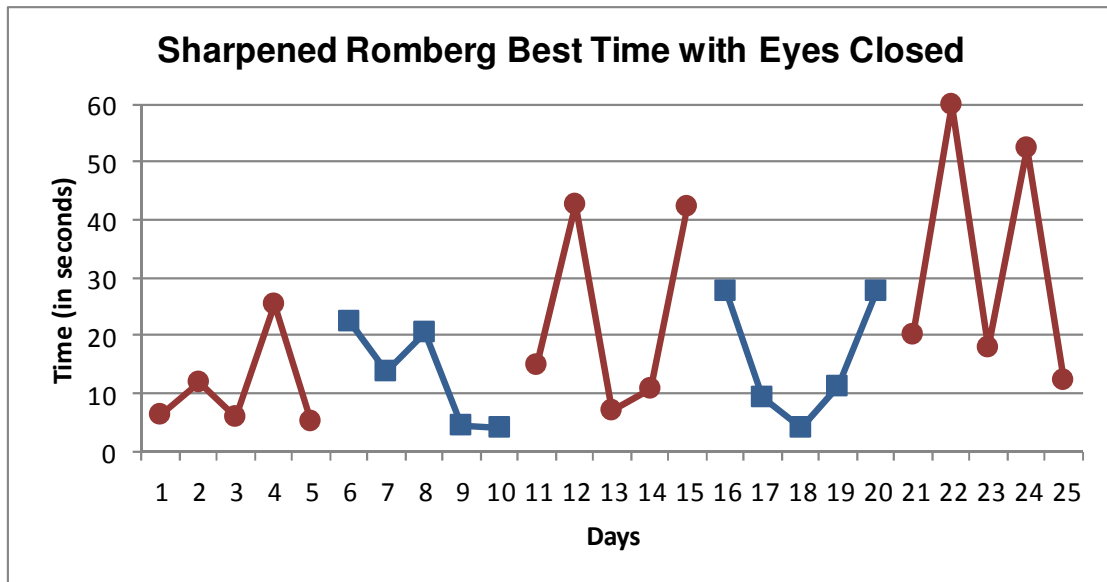
Phase 4

Level: High
Trend: Stable
Variability: None
Immediacy of effect: N/A (ceiling effect)
Data overlap (phase 3 to 4)
PND: 0%
PEM: 100%
PEAv: 100%
PDO: (5+5+5+5+0/25) 80%
Consistency: Very high

Phase 5

Level: High
Trend: Stable
Variability: Low
Immediacy of effect: None
Data overlap (phase 4 to 5):
PND: 20%
PEM: 20%
PEAv: 20%
PDO: (1+1+1+1+1/25) 20%
Consistency: None

*Eyes Closed Sharpened Romberg



Phase 1

Level: Low to medium
Trend: N/A
Variability: Medium/low

Phase 2

Level: Medium to low
Trend: Decreasing
Variability: Slight
Immediacy of effect: None
Data overlap (phase 1 to 2):
PND: 0%
PEM: 60%
PEAv: 60%
PDO: (3+3+3+0+3/25) 48%

Phase 3

Level: Medium to low
Trend: N/A due to instability
Variability: High
Immediacy of effect: None
Data overlap (phase 2 to 3):
PND: 0%
PEM: 40%
PEAv: 40%
PDO: (3+2+3+0+0/25) 32%
Consistency: None

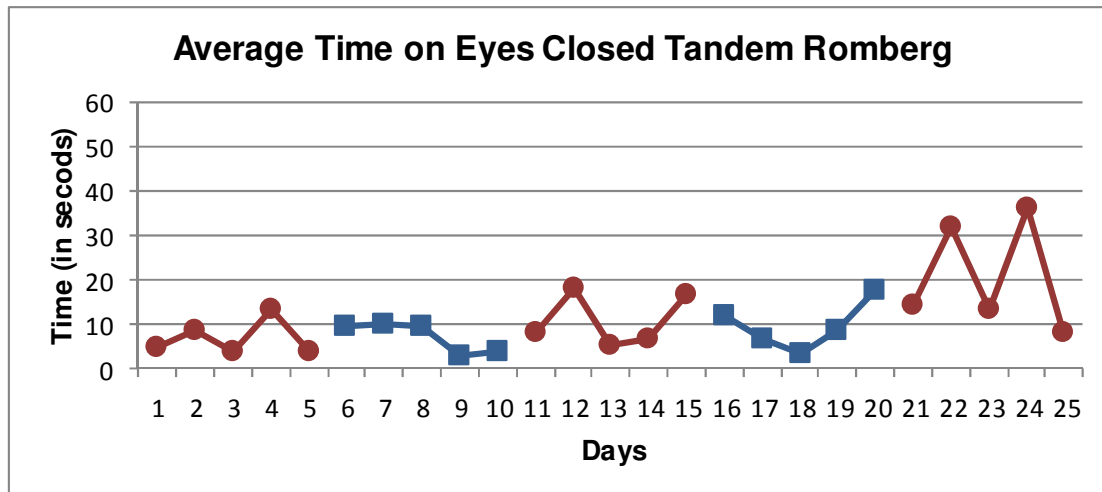
Phase 4

Level: Medium to low
Trend: Curvilinear
Variability: Curvilinear
Immediacy of effect: None
Data overlap (phase 3 to 4):
PND: 0%
PEM: 40%
PEAv: 40%
PDO: (2+0+4+3+0/25) 36%
Consistency: None

Phase 5

Level: Medium to high
Trend: N/A due to instability
Variability: High
Immediacy of effect: None
Data overlap (phase 4 to 5):
PND: 0%
PEM: 0%
PEAv: 20%
PDO: (3+0+0+0+3/25) 24%
Consistency: Moderate

Average Eyes Closed Sharpened Romberg Scores



Phase 1

Level: Low
Trend: Stable
Variability: Slight

Phase 2

Level: Low
Trend: Decreasing slightly
Variability: Low to moderate
Immediacy of effect: None
Data overlap (phase 1 to 2):
PND: 0%
PEM: 60%
PEAv: 60%
PDO: (3+3+3+0+3/25) 48%

Phase 3

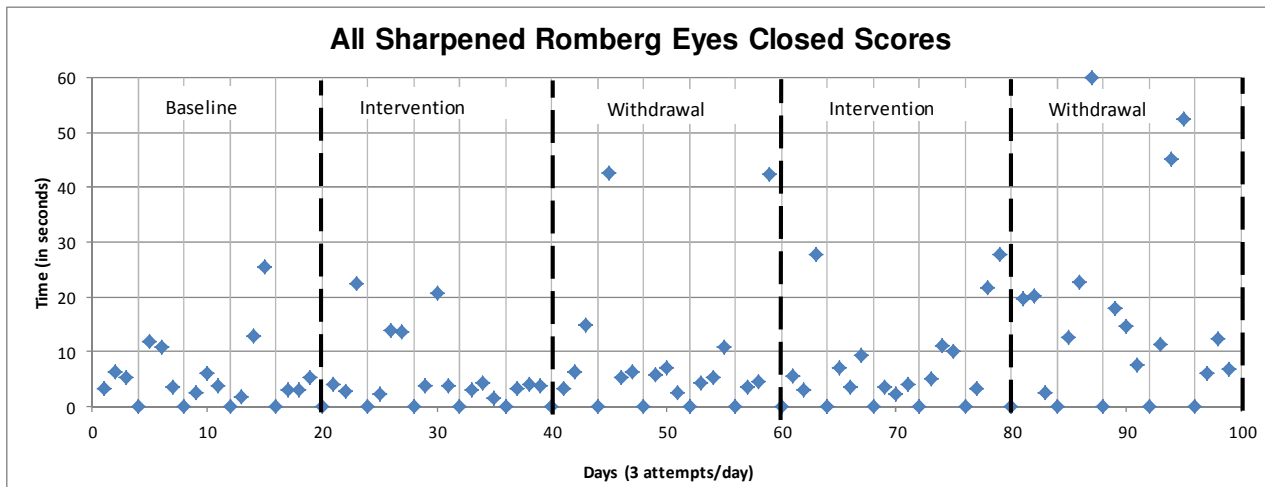
Level: Low
Trend: N/A due to instability
Variability: Moderate
Immediacy of effect: None
Data overlap (phase 2 to 3):
PND: 0%
PEM: 60%
PEAv: 40%
PDO: (3+3+3+0+0/25) 36%
Consistency: Moderate

Phase 4

Level: Low
Trend: Curvilinear
Variability: Curvilinear
Immediacy of effect: None
Data overlap (phase 3 to 4):
PND: 0%
PEM: 40%
PEAv: 40%
PDO: (2+0+4+3+1/25) 40%
Consistency: None

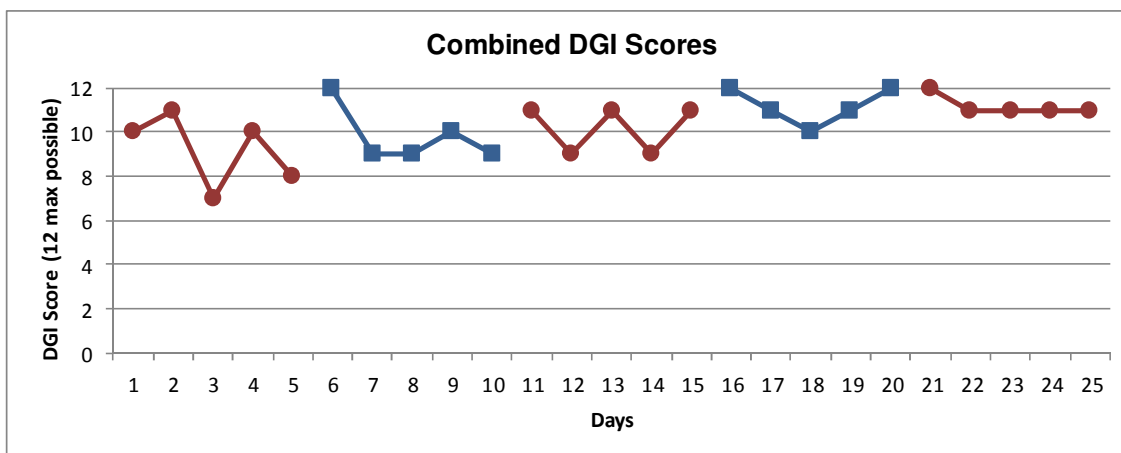
Phase 5

Level: Medium to low
Trend: N/A due to instability
Variability: High
Immediacy of effect: None
Data overlap (phase 4 to 5):
PND: 0%
PEM: 0%
PEAv: 20%
PDO: (1+0+0+1+3/25) 20%
Consistency: None

***All Scores from Eyes Closed Sharpened Romberg**

The raw data for the Sharpened Romberg with eyes closed was included as an additional way to view and understand the data. Formal analyses were not completed on this graph. Trends noted appear to include an increase in variability of the data, particularly in the final phase.

*Combined Dynamic Gait Index Scores



Phase 1

Level: Medium to high
Trend: N/A due to instability, decreasing slightly
Variability: Medium to high

Phase 2

Level: Medium to high
Trend: N/A
Variability: Medium
Immediacy of effect: N/A
Data overlap (phase 1 to 2):
PND: 20%
PEM: 20%
PEAv: 40%
PDO: (1+1+5+1+5/25) 52%

Phase 3

Level: Medium to high
Trend: N/A due to instability
Variability: High
Immediacy of effect: N/A
Data overlap (phase 2 to 3):
PND: 0%
PEM: 0%
PEAv: 0%
PDO: (5+0+0+2+0/25) 28%
Consistency: Moderate

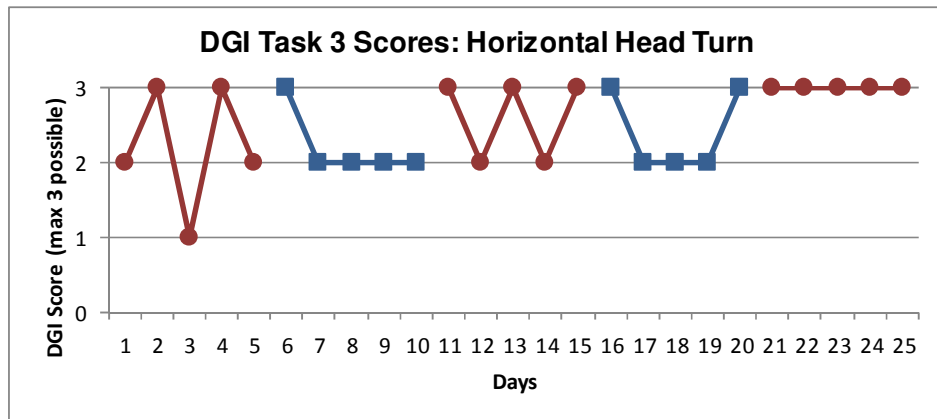
Phase 4

Level: N/A
Trend: Curvilinear
Variability: Curvilinear
Immediacy of effect: N/A
Data overlap (phase 3 to 4):
PND: 40%
PEM: 40%
PEAv: 80%
PDO: (2+5+2+5+2/25) 64%
Consistency: Very low

Phase 5

Level: High
Trend: Stable
Variability: Low
Immediacy of effect: N/A
Data overlap (phase 4 to 5):
PND: 0%
PEM: 0%
PEAv: 80%
PDO: (4+0+0+0+4/25) 32%
Consistency: Low

Dynamic Gait Index Individual Task Scores



For the analysis of individual DGI tasks, there is a three point scale, therefore, any change in rating indicates higher variability than on the combined DGI scores with a greater possible overall score where a difference of 1 is not as significant. It is possible that a change of one point on individual tasks indicates a change in function. If a modified scale had been used to rate the DGI tasks there may have been less variability in scores and trends may have been easier to identify.

Phase 1

Level: N/A due to instability

Trend: N/A due to instability

Variability: High

Phase 2

Level: Moderate/High

Trend: Stable

Variability: Low

Immediacy of effect: N/A

Data overlap (phase 1 to 2):

PND: 0%

PEM: 20%

PEAv: 20%

PDO: (1+0+5+0+1/25) 28%

Phase 3

Level: High/Moderate

Trend: N/A due to instability

Variability: High

Immediacy of effect: N/A

Data overlap (phase 2 to 3):

PND: 0%

PEM: 0%

PEAv: 40%

PDO: (2+0+0+0+0/25) 8%

Consistency: Moderate/High

Phase 4

Level: Moderate/High

Trend: N/A

Variability: Moderate

Immediacy of effect: N/A

Data overlap (phase 3 to 4):

PND: 0%

PEM: 0%

PEAv: 40%

PDO: (0+2+0+2+0/25) 16%

Consistency: High

Phase 5

Level: High

Trend: Stable

Variability: None

Immediacy of effect: N/A

Data overlap (phase 2 to 3):

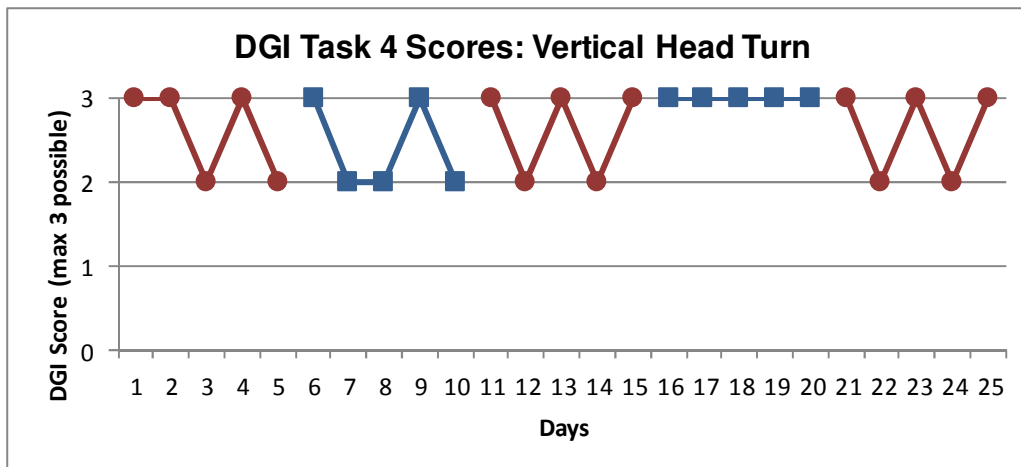
PND: 0%

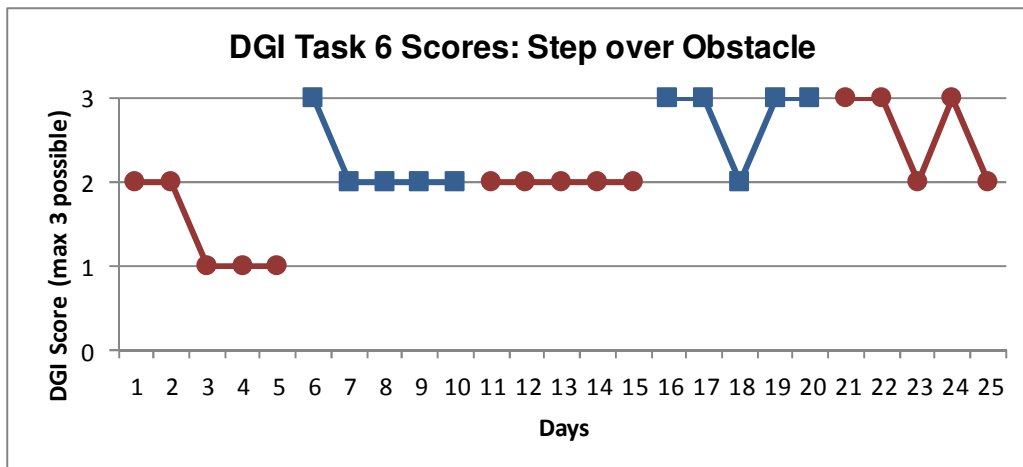
PEM: 0%

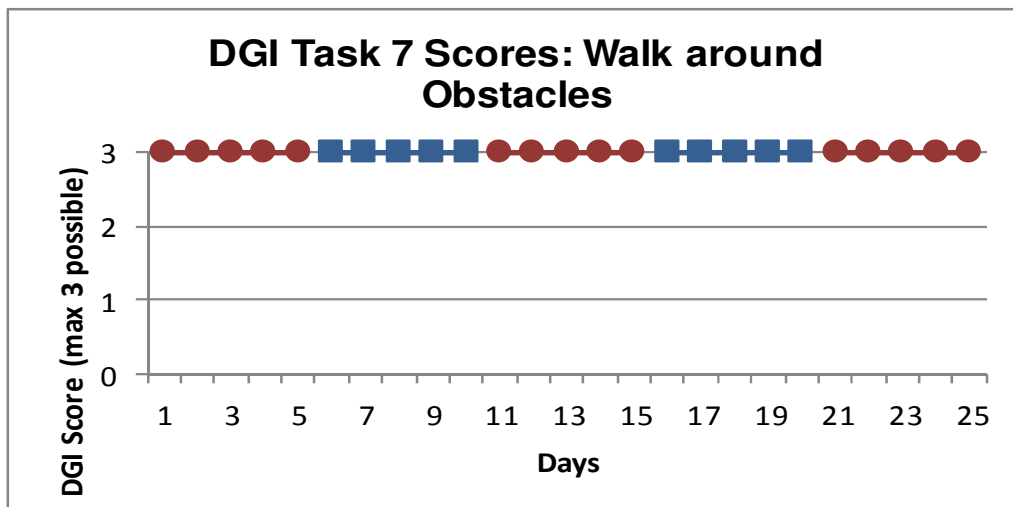
PEAv: 0%

PDO: (0+0+0+0+0/25) 0%

Consistency: Low

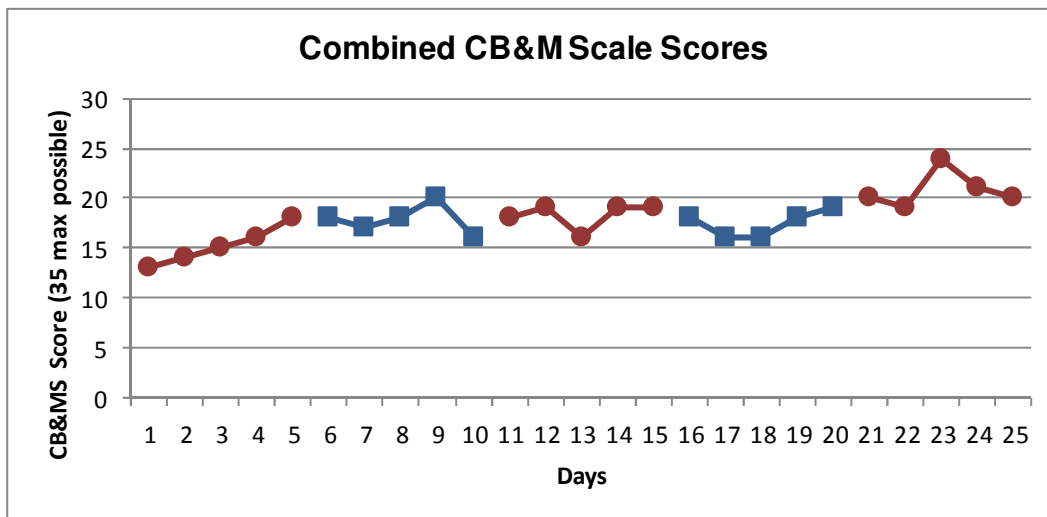
**Phase 1**Level: High/ModerateTrend: N/AVariability: High**Phase 2**Level: Moderate/HighTrend: N/AVariability: HighImmediacy of effect: N/AData overlap (phase 1 to 2):PND: 0%PEM: 0%PEAv: 40%PDO: (0+0+2+0+2/25) 16%**Phase 3**Level: High/ModerateTrend: N/AVariability: HighImmediacy of effect: N/AData overlap (phase 2 to 3):PND: 0%PEM: 0%PEAv: 40%PDO: (2+0+0+2+0/25) 16%Consistency across phases: High consistency, both have similar variability and patterns**Phase 4**Level: HighTrend: StableVariability: NoneImmediacy of effect: N/AData overlap (phase 3 to 4):PND: 0%PEM: 0%PEAv: 100%PDO: (0+5+0+5+0/25) 40%Consistency across phases: Low**Phase 5**Level: High/ModerateTrend: N/AVariability: HighImmediacy of effect: N/AData overlap (phase 4 to 5):PND: 0%PEM: 40%PEAv: 40%PDO: (2+2+2+2+2/25) 40%Consistency: Complete

**Phase 1**Level: Moderate/LowTrend: N/AVariability: Moderate**Phase 2**Level: Moderate/HighTrend: StableVariability: LowImmediacy of effect: MildData overlap (phase 1 to 2):PND: 20%PEM: 100%PEAv: 100%PDO: (1+1+5+5+5/25) 68%**Phase 3**Level: ModerateTrend: StableVariability: NoneImmediacy of effect: N/AData overlap (phase 2 to 3):PND: 0%PEM: 0%PEAv: 100%PDO: (5+0+0+0+0/25) 20%Consistency across phases: Low**Phase 4**Level: HighTrend: StableVariability: LowImmediacy of effect: MildData overlap (phase 3 to 4):PND: 80%PEM: 80%PEAv: 80%PDO: (4+4+4+4+4/25) 80%Consistency: N/A to low**Phase 5**Level: High/ModerateTrend: N/AVariability: HighImmediacy of effect: N/AData overlap (phase 4 to 5):PND: 0%PEM: 40%PEAv: 40%PDO: (2+2+0+2+2/25) 32%Consistency: Low



All data points for Task 7 of the DGI (walking around obstacles) reached the maximum score on each day of the study (3 out of 3). Therefore, no data analysis was completed or necessary.

Combined Community Balance & Mobility Scale Scores



Phase 1

Level: Moderate
Trend: Increasing slightly
Variability: Low

Phase 2

Level: Moderate
Trend: None
Variability: Moderate
Immediacy of effect: None
Data overlap (phase 1 to 2):
PND: 20%
PEM: 100%
PEAv: 100%
PDO: (5+5+5+4+1/25) 80%

Phase 3

Level: Moderate
Trend: Stable
Variability: Low
Immediacy of effect: None
Data overlap (phase 2 to 3):
PND: 0%
PEM: 20%
PEAv: 20%
PDO: (1+1+1+5+0/25) 32%
Consistency: None

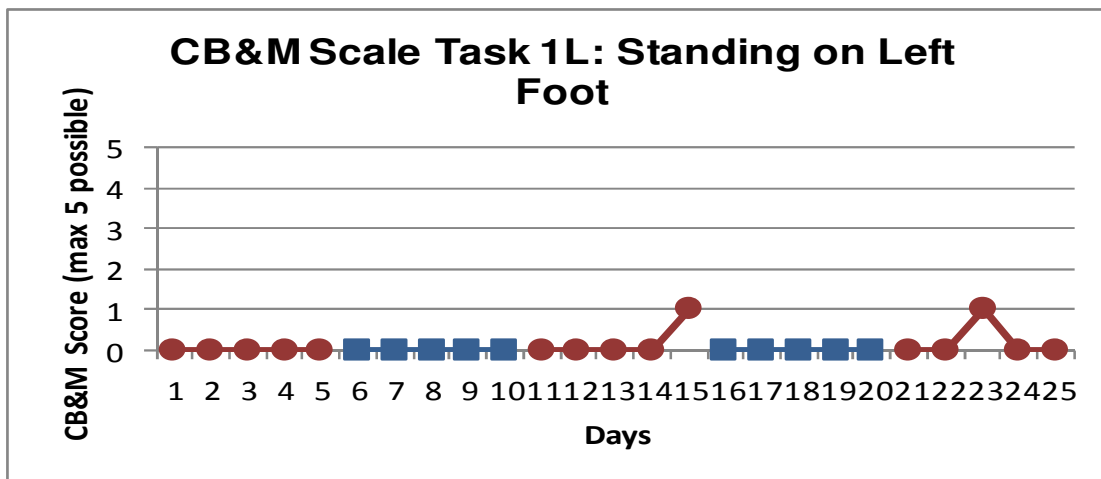
Phase 4

Level: Moderate
Trend: Increasing slightly
Variability: Low
Immediacy of effect: None
Data overlap (phase 3 to 4):
PND: 0%
PEM: 0%
PEAv: 20%
PDO: (1+0+3+0+0/25) 16%
Consistency: Moderate

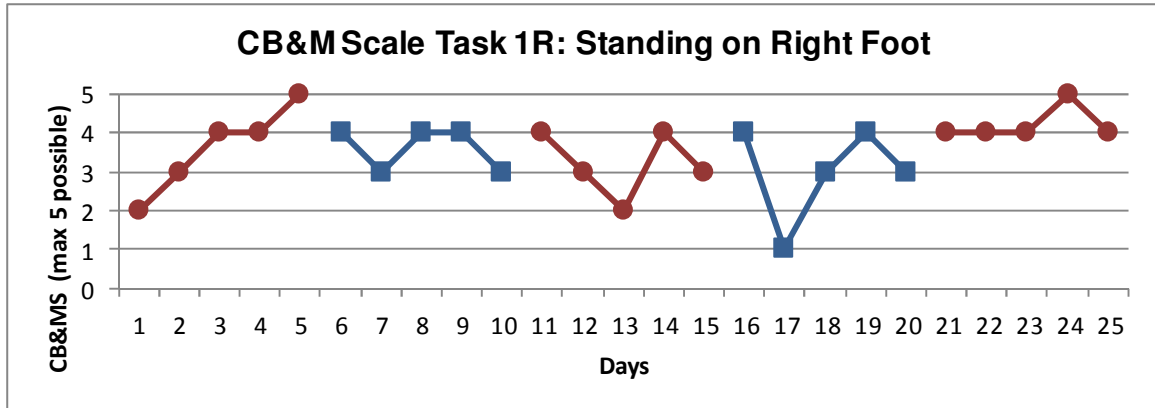
Phase 5

Level: Moderate
Trend: None
Variability: Moderate
Immediacy of effect: None
Data overlap (phase 4 to 5):
PND: 0%
PEM: 0%
PEAv: 0%
PDO: (0+0+0+0+0/25) 0%
Consistency: Low

Community Balance & Mobility Scale Individual Task Scores



All data points for the first task on the CB&M Scale (Standing on the left foot) were the lowest possible score, indicating an inability to complete the task, each day of the study except two. Further analysis was not completed or necessary for this data.

**Phase 1**

Level: N/A
Trend: Increasing
Variability: Low

Phase 2

Level: Moderate
Trend: Stable
Variability: Moderate
Immediacy of effect: N/A
Data overlap (phase 1 to 2):
PND: 0%
PEM: 0%
PEAv: 60%
PDO: (5+3+0+0+0/25) 32%

Phase 3

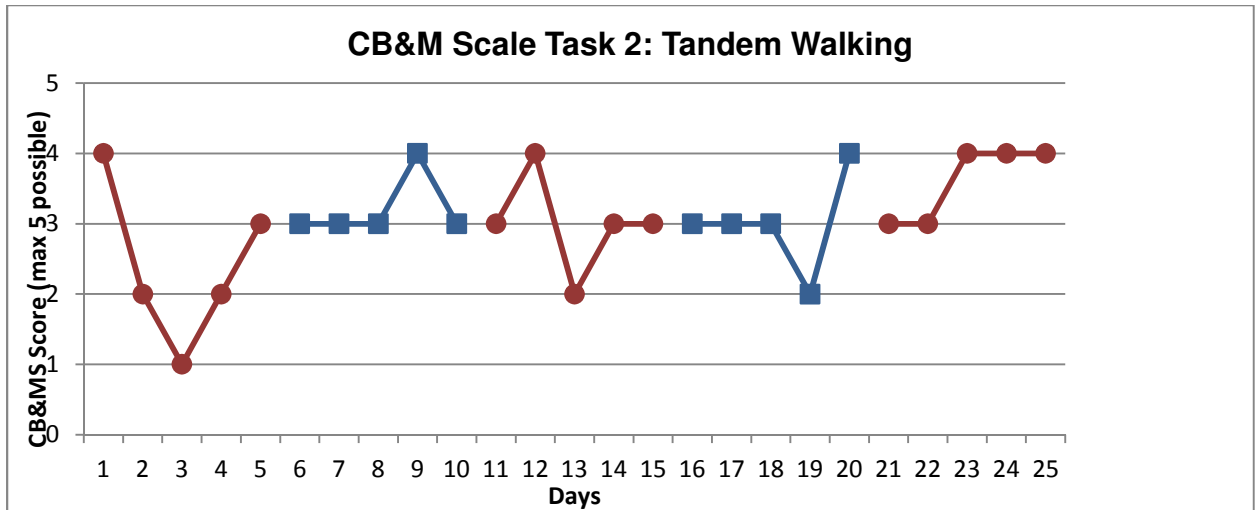
Level: Moderate
Trend: N/A
Variability: High
Immediacy of effect: N/A
Data overlap (phase 2 to 3):
PND: 20%
PEM: 0%
PEAv: 60%
PDO: (3+1+3+3+1/25) 44%
Consistency: None

Phase 4

Level: N/A
Trend: N/A
Variability: High
Immediacy of effect: N/A
Data overlap (phase 3 to 4):
PND: 0%
PEM: 40%
PEAv: 40%
PDO: (0+2+4+0+2/25) 32%
Consistency: None

Phase 5

Level: High/Moderate
Trend: Stable
Variability: Low
Immediacy of effect: N/A
Data overlap (phase 4 to 5):
PND: 0%
PEM: 0%
PEAv: 0%
PDO: (0+0+0+0+0/25) 0%
Consistency: None

**Phase 1**

Level: N/A
Trend: N/A
Variability: High

Phase 2

Level: Moderate
Trend: Stable
Variability: Low
Immediacy of effect: N/A
Data overlap (phase 1 to 2):
PND: 0%
PEM: 100%
PEAv: 100%
PDO: (0+5+5+5+1/25) 64%

Phase 3

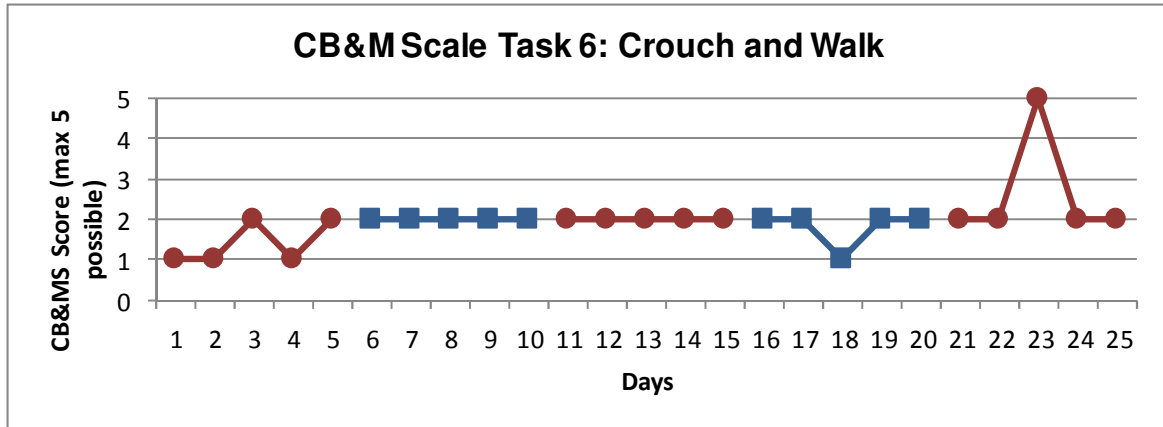
Level: Moderate
Trend: Stable
Variability: Moderate
Immediacy of effect: N/A
Data overlap (phase 2 to 3):
PND: 20%
PEM: 20%
PEAv: 80%
PDO: (1+1+1+4+1/25) 32%
Consistency: None

Phase 4

Level: Moderate
Trend: Stable
Variability: Moderate
Immediacy of effect: N/A
Data overlap (phase 3 to 4):
PND: 0%
PEM: 20%
PEAv: 20%
PDO: (1+0+4+1+1/25) 28%
Consistency: Moderate

Phase 5

Level: Moderate
Trend: Stable
Variability: Moderate
Immediacy of effect: N/A
Data overlap (phase 4 to 5):
PND: 0%
PEM: 0%
PEAv: 0%
PDO: (0+0+0+0+2/25) 8%
Consistency: Low

**Phase 1**

Level: Low
Trend: Stable
Variability: Low/Moderate

Phase 2

Level: Low
Trend: Stable
Variability: None
Immediacy of effect: N/A
Data overlap (phase 1 to 2):
PND: 0%
PEM: 100%
PEAv: 100%
PDO: (5+5+0+5+0/25) 60%

Phase 3

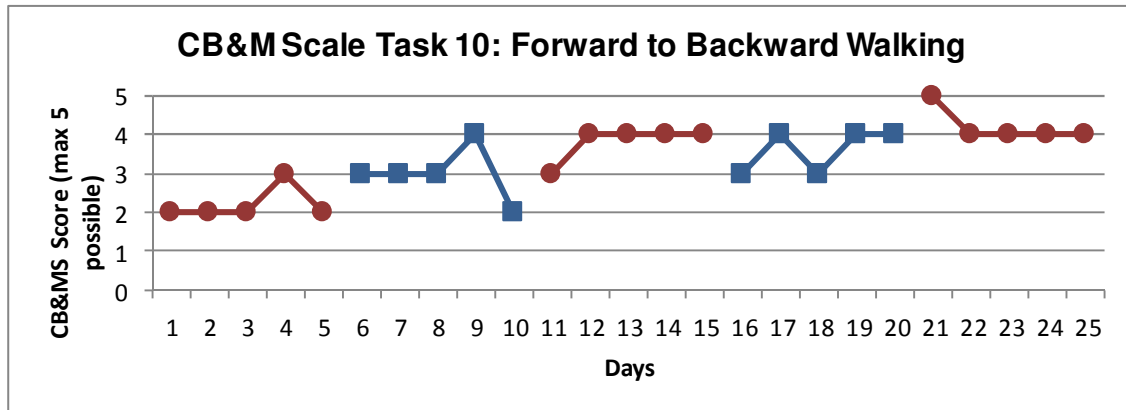
Level: Low
Trend: Stable
Variability: None
Immediacy of effect: N/A
Data overlap (phase 2 to 3):
PND: 0%
PEM: 0%
PEAv: 0%
PDO: (0+0+0+0+0/25) 0%
Consistency: Low

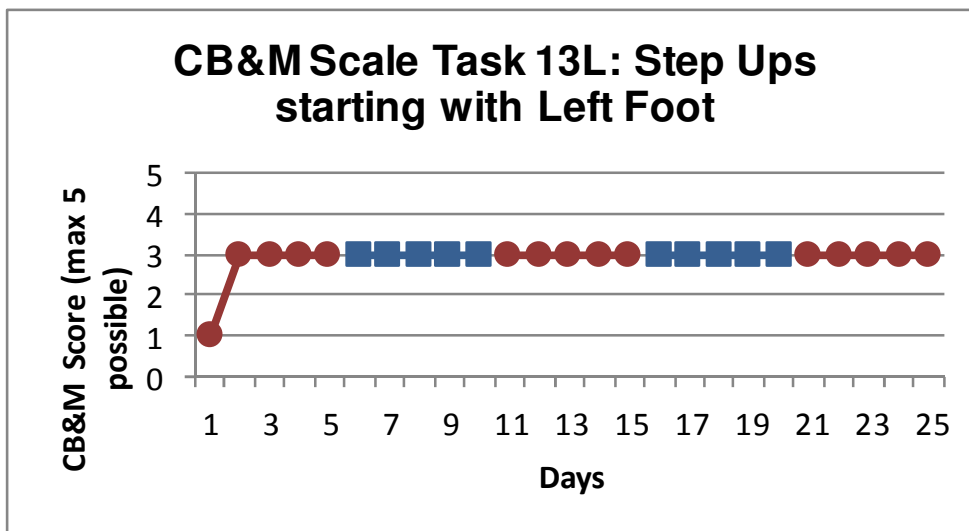
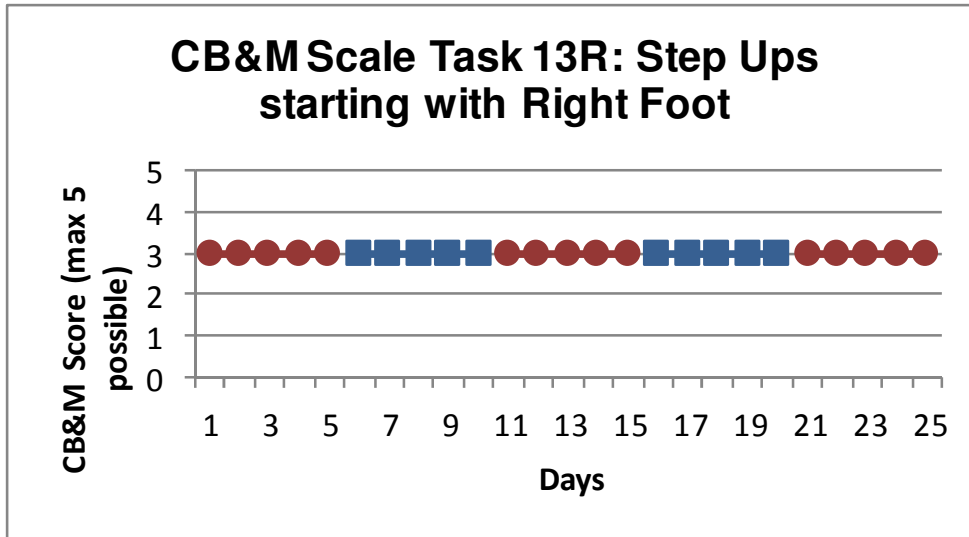
Phase 4

Level: Low
Trend: Stable
Variability: Low
Immediacy of effect: N/A
Data overlap (phase 3 to 4):
PND: 0%
PEM: 0%
PEAv: 0%
PDO: (0+0+0+0+0/25) 0%
Consistency across phases: High

Phase 5

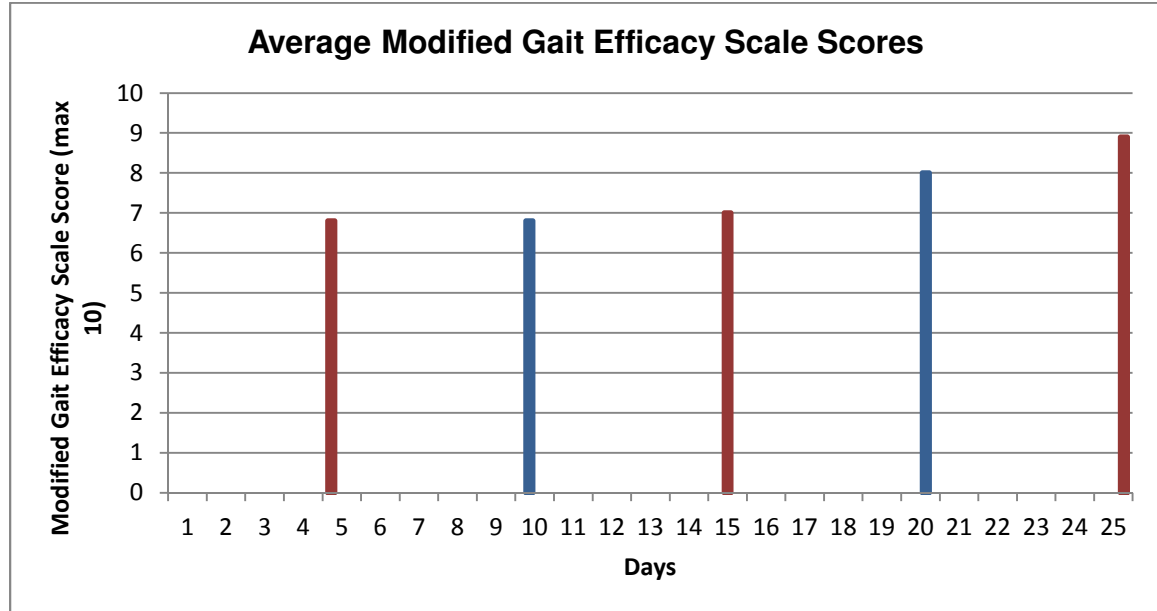
Level: Low
Trend: Stable
Variability: Moderate
Immediacy of effect: N/A
Data overlap (phase 4 to 5):
PND: 0%
PEM: 0%
PEAv: 0%
PDO: (0+0+0+0+0/25) 0%
Consistency: High

**Phase 1**Level: Low/ModerateTrend: StableVariability: Low**Phase 2**Level: ModerateTrend: StableVariability: ModerateImmediacy of effect: N/AData overlap (phase 1 to 2):PND: 20%PEM: 80%PEAv: 80%PDO: (4+4+4+1+4/25) 68%**Phase 3**Level: ModerateTrend: StableVariability: LowImmediacy of effect: N/AData overlap (phase 2 to 3):PND: 0%PEM: 0%PEAv: 0%PDO: (0+0+0+1+0/25) 8%Consistency across phases: Low**Phase 4**Level: ModerateTrend: StableVariability: ModerateImmediacy of effect: N/AData overlap (phase 3 to 4):PND: 0%PEM: 0%PEAv: 60%PDO: (3+0+0+0+0/25) 12%Consistency: Moderate**Phase 5**Level: Moderate/HighTrend: StableVariability: LowImmediacy of effect: N/AData overlap (phase 4 to 5):PND: 0%PEM: 0%PEAv: 0%PDO: (0+0+0+0+0/25) 0%Consistency: High



All data points for Task 13 of the CB&M Scale (Step Ups onto a single stair) received a 3 out of 5 on each day of the study when leading with the right foot. When leading with the left foot, each day after the first day was scored the same at 3 out of 5. Therefore, no data analysis was completed or necessary as the data had no changes.

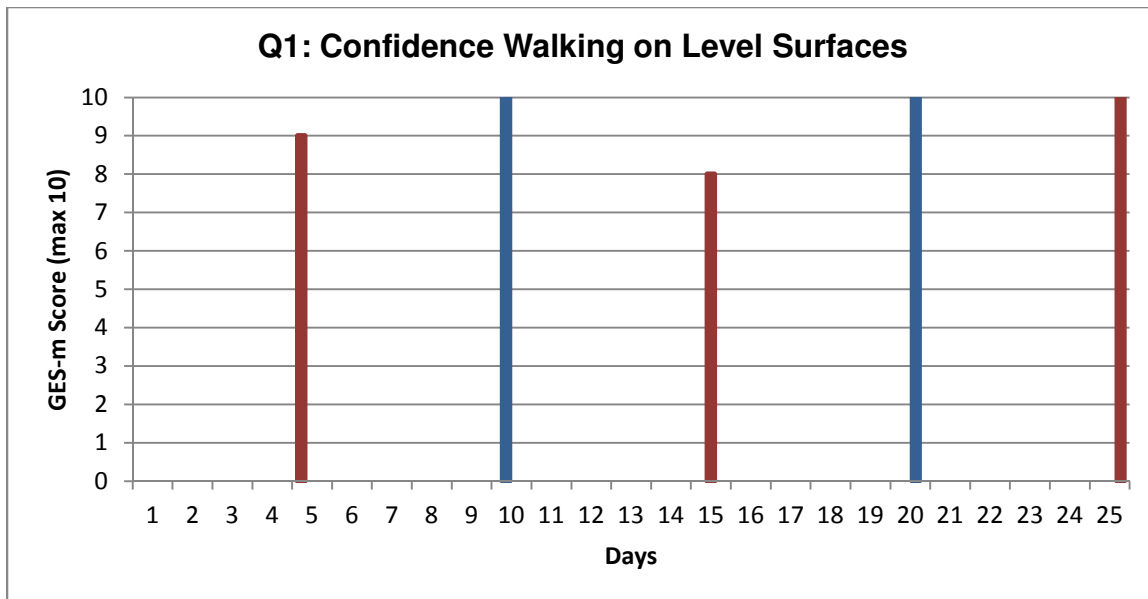
Average Modified Gait Efficacy Scale Scores



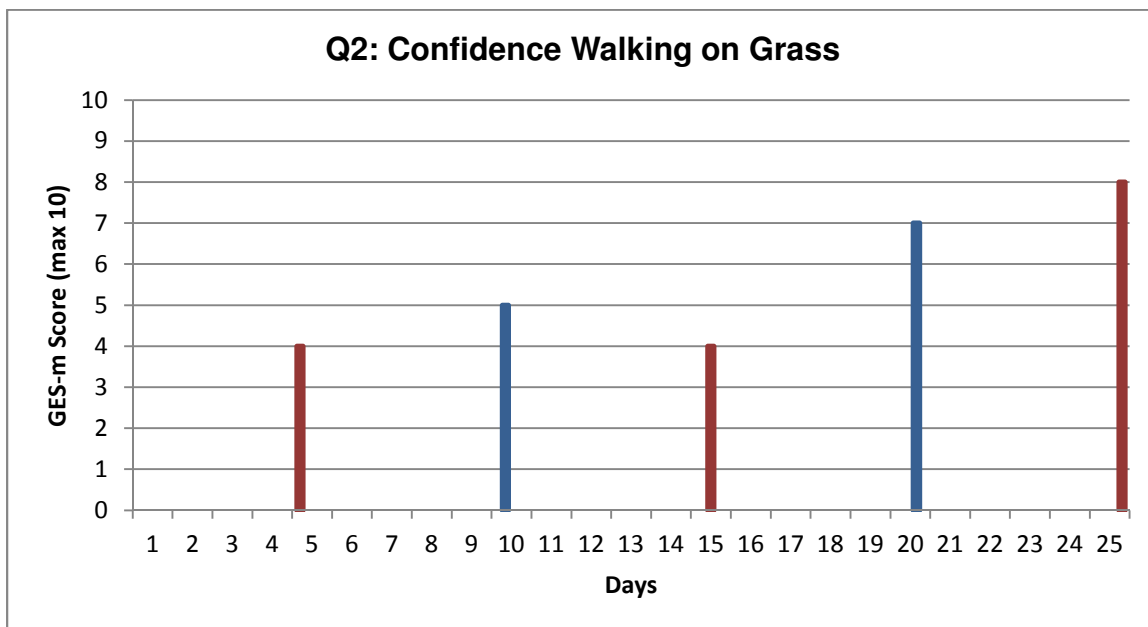
The average score on the ten question modified Gait Efficacy Scale for each week was plotted. The participant's average confidence on the GES-m remained stable the first two weeks, increased very slightly the third week then increased one point in the second intervention phase and increased one point in the second withdrawal phase.

None of the changes in scores for the average GES-m or individual questions were significant based on the true change scores for the mGES (6 points).

No statistical analyses were completed on the modified Gait Efficacy Scale questions as they were only completed once weekly. Trends in scores can be observed visually.

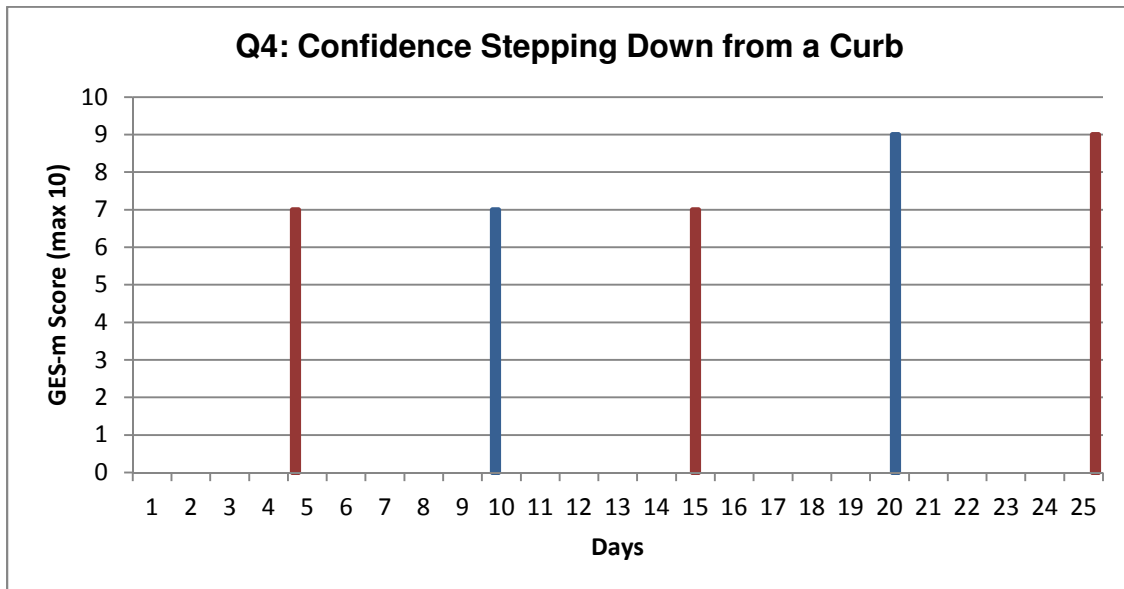
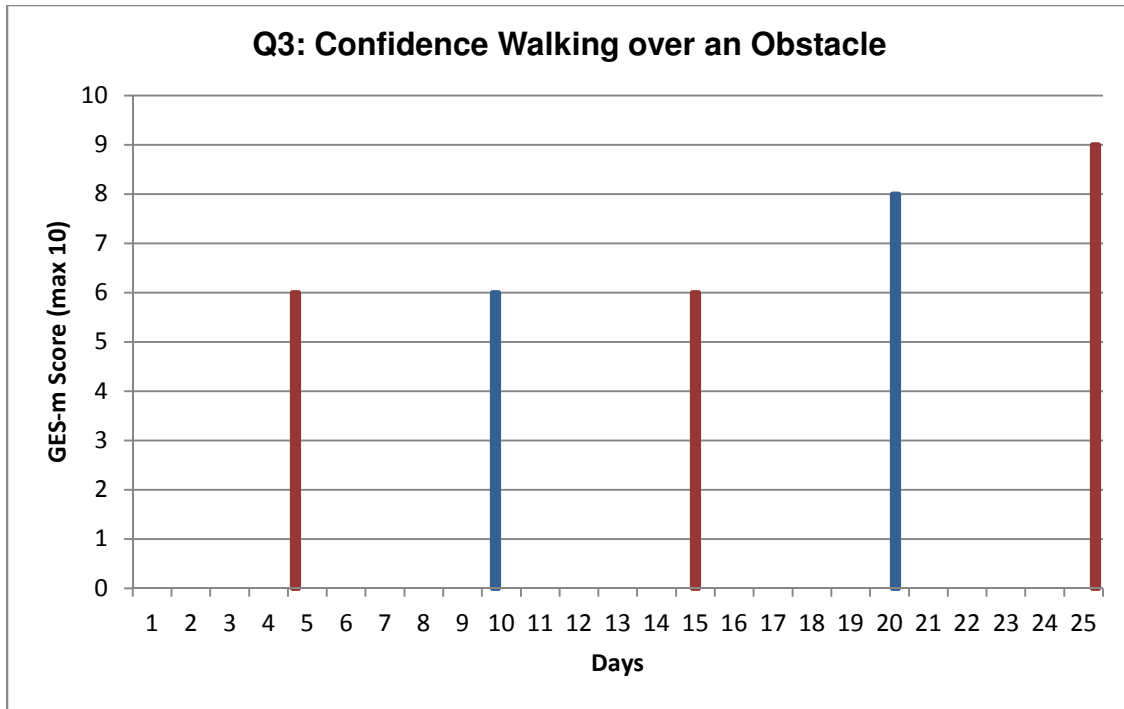


*

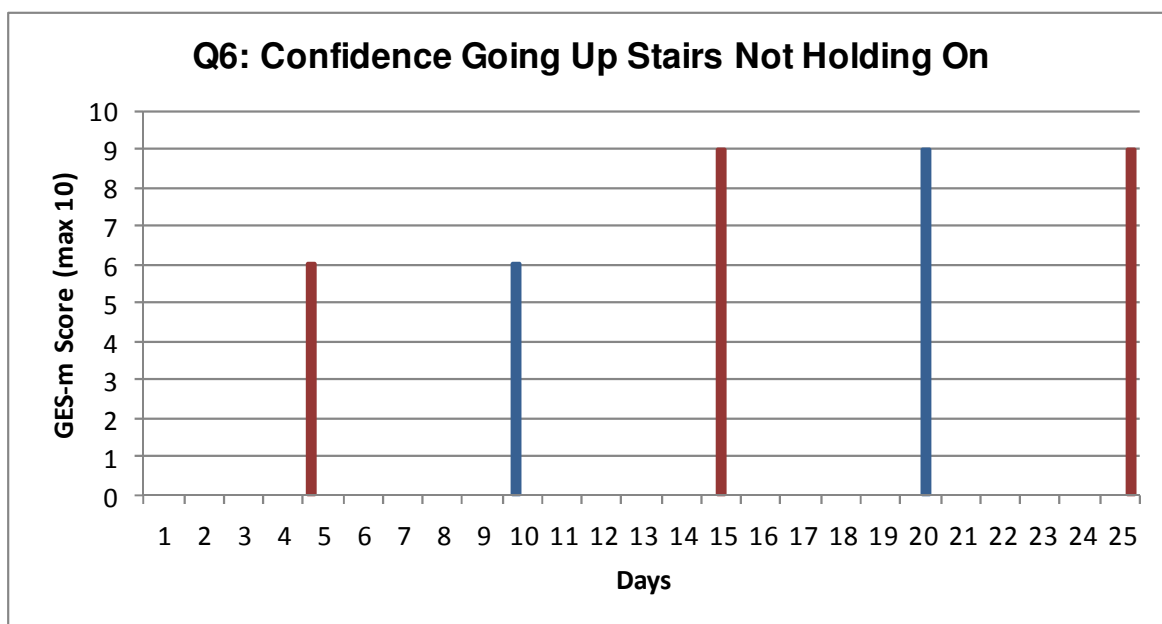
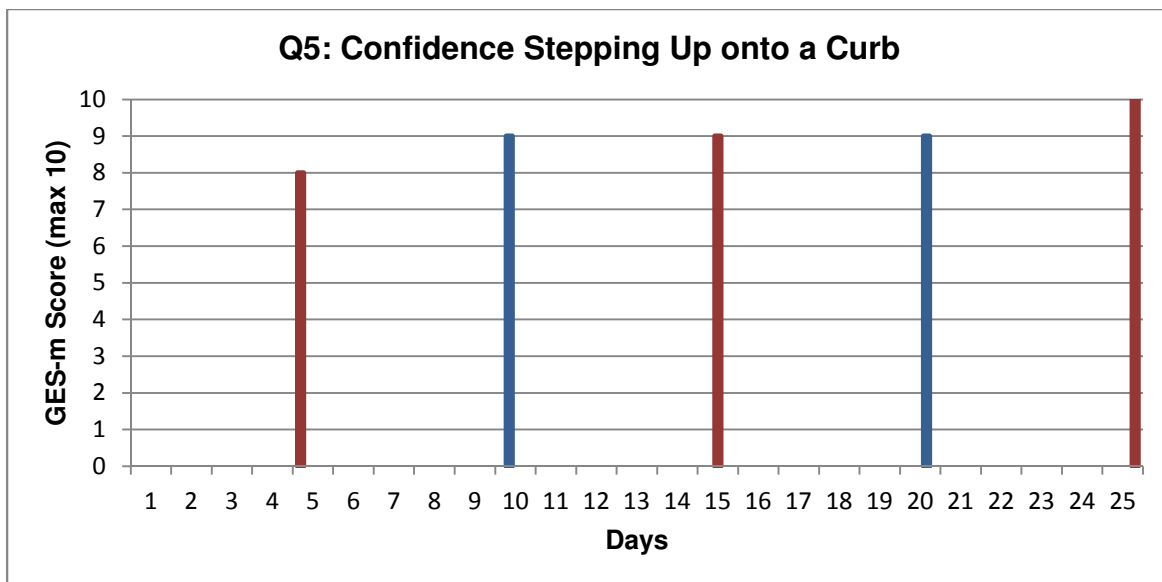


Confidence on the first question (walking on level surfaces) increased during the both intervention weeks to maximum possible confidence, decreased during the first withdrawal week, and stayed at the maximum confidence for the second withdrawal week.

*The second question (walking on grass) shows the same pattern as the first, with confidence increasing during the first intervention week, decreasing back to the baseline for the first withdrawal, increasing again in the second intervention week, and increasing further during the second withdrawal week.

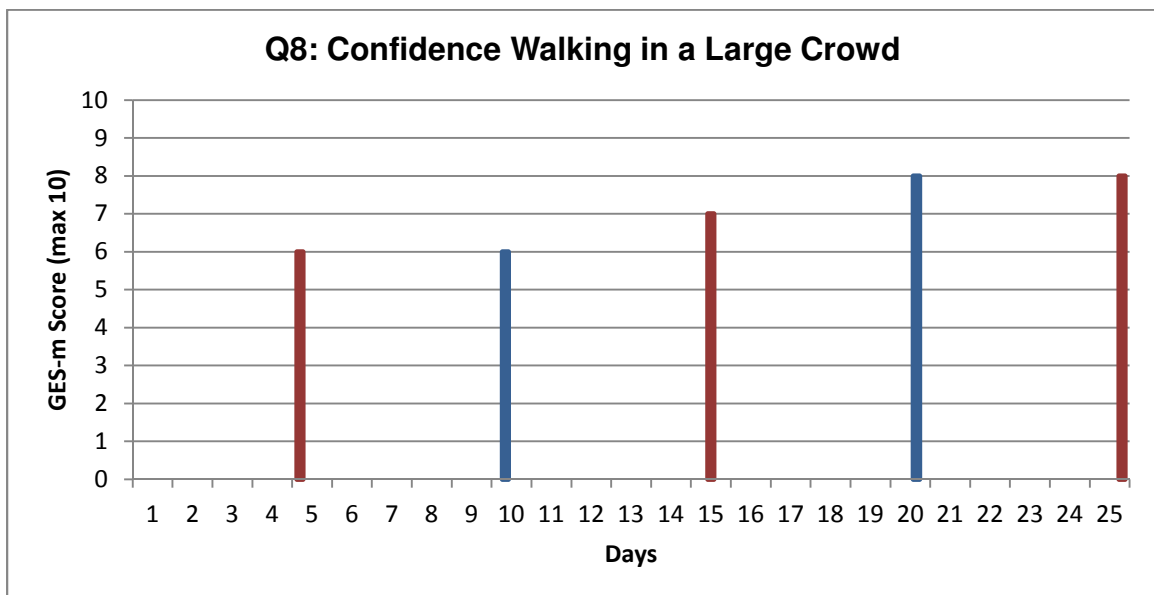
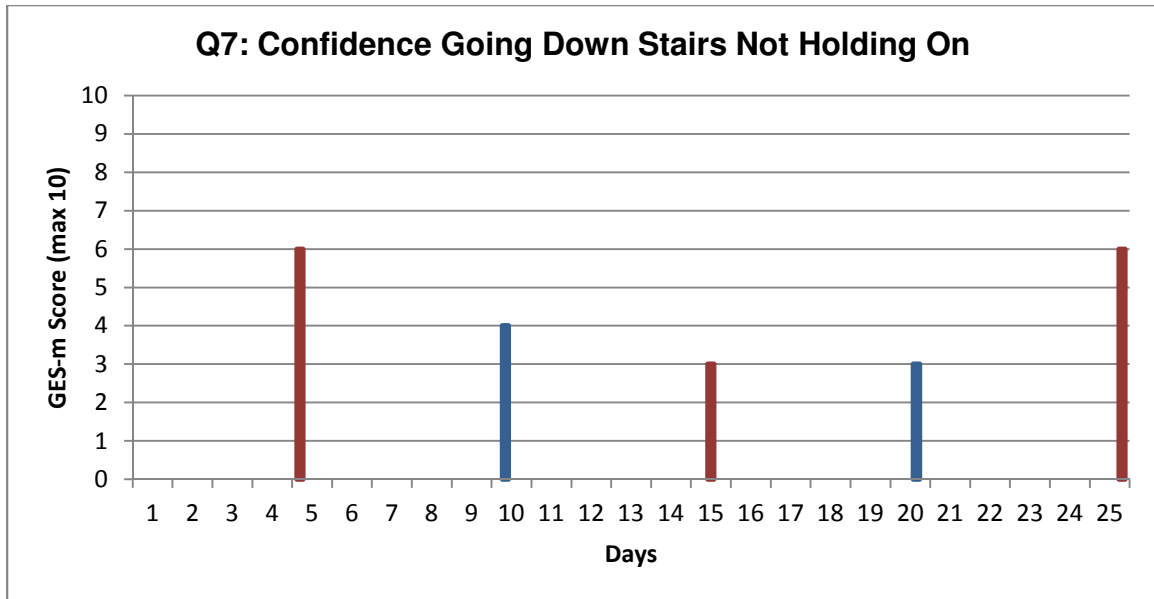


Confidence on the third question (walking over an obstacle) remained constant for the first three weeks, increased two points after the second intervention week, and increased another point after the second withdrawal week. Confidence on the fourth question (stepping down from a curb) also remained stable the first three weeks before increasing two points after the second intervention week and remaining stable there after the second withdrawal week.



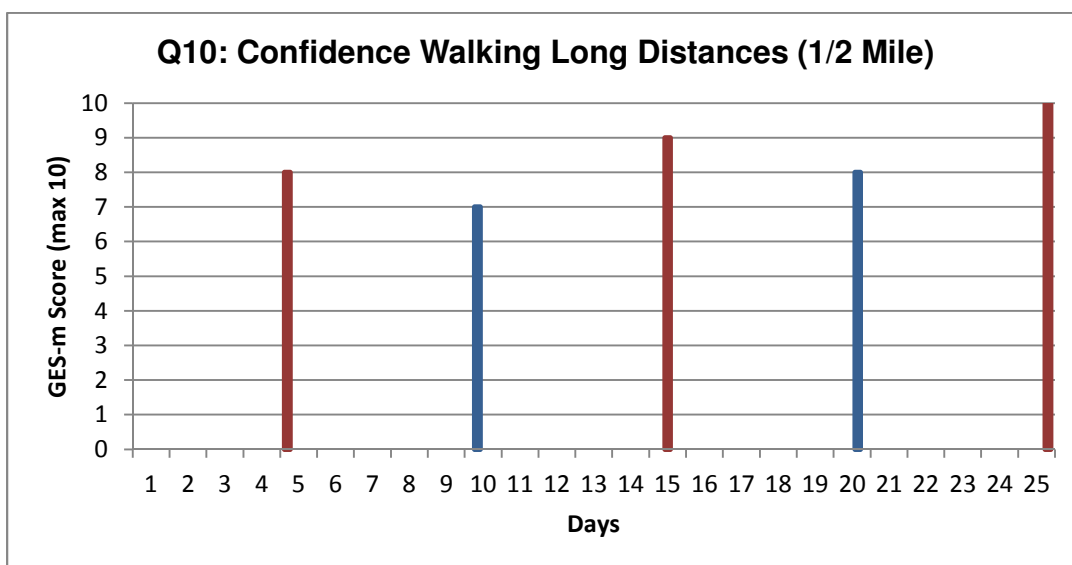
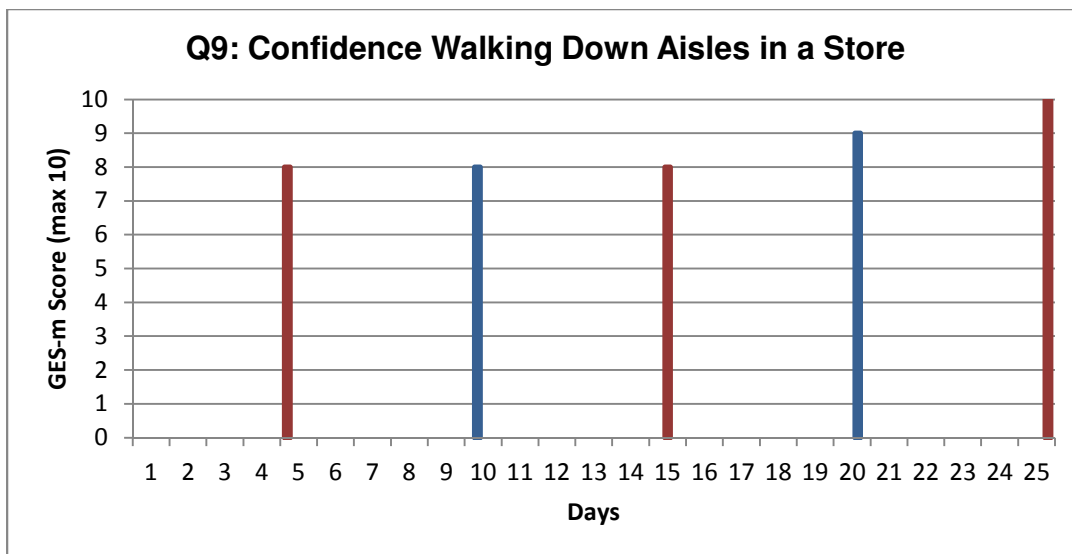
Confidence on the fifth question (stepping up onto a curb) increased one point after the first intervention week, remained stable there for three weeks, then increase one more point after the second withdrawal week.

Confidence on the sixth question (going up stairs without holding on) remained stable during the first two weeks, increased three points after the first withdrawal week and remained stable there the rest of the study.



Confidence on the seventh task (going down stairs without holding on) decreased two points after the first intervention week, decreased another point after the first withdrawal week, remained stable after the second intervention week, and increased three points after the second withdrawal week (returning to baseline confidence level).

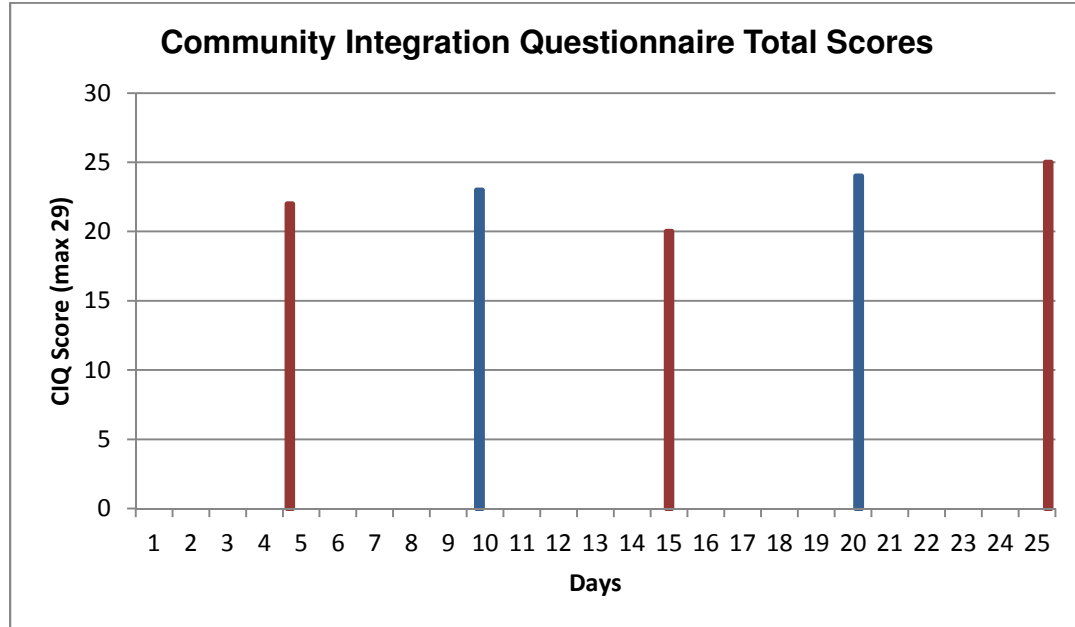
Confidence on the eighth task (walking in a large crowd) remained stable the first two weeks, increased one point after the first withdrawal week, increased another point after the second intervention week, and remained stable there after the second withdrawal week.



Confidence on the ninth task (walking down aisles in a store) remained constant the first three weeks, increased one point after the second intervention week, and increased another point after the second withdrawal week.

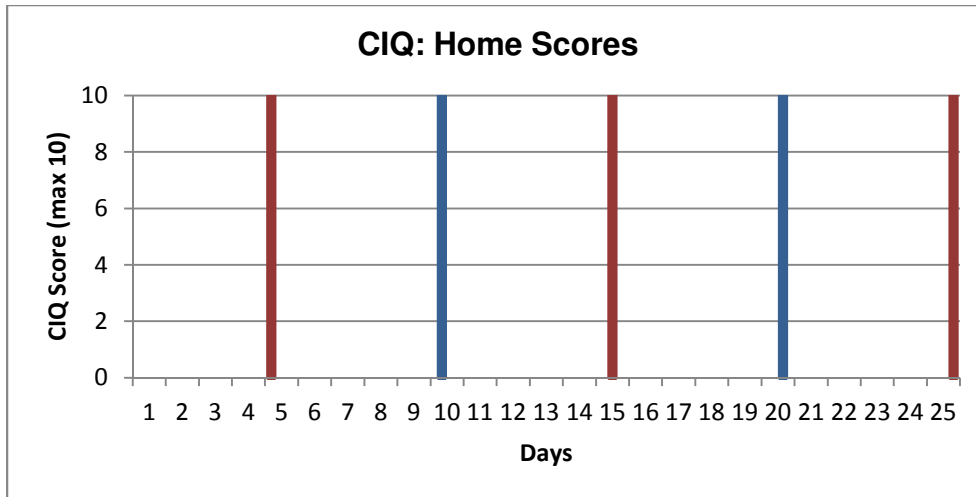
Confidence on the tenth task (walking long distances like 1/2 mile) decreased one point after the first intervention session, increased two points after the first withdrawal week, decreased one point after the second intervention week, and increased two points after the second withdrawal week. The responses to this question are particularly interesting as they do not correlate with the statements made by the participant throughout the study. The participant indicated several times during intervention weeks that walking had not felt as natural or confident in years, and he noted he usually experienced pain when walking long distances prior to the study. However, when he was completing the treadmill activities, he often remarked that the walking felt very good and he wanted to continue walking either on the treadmill or around the office building.

Community Integration Questionnaire

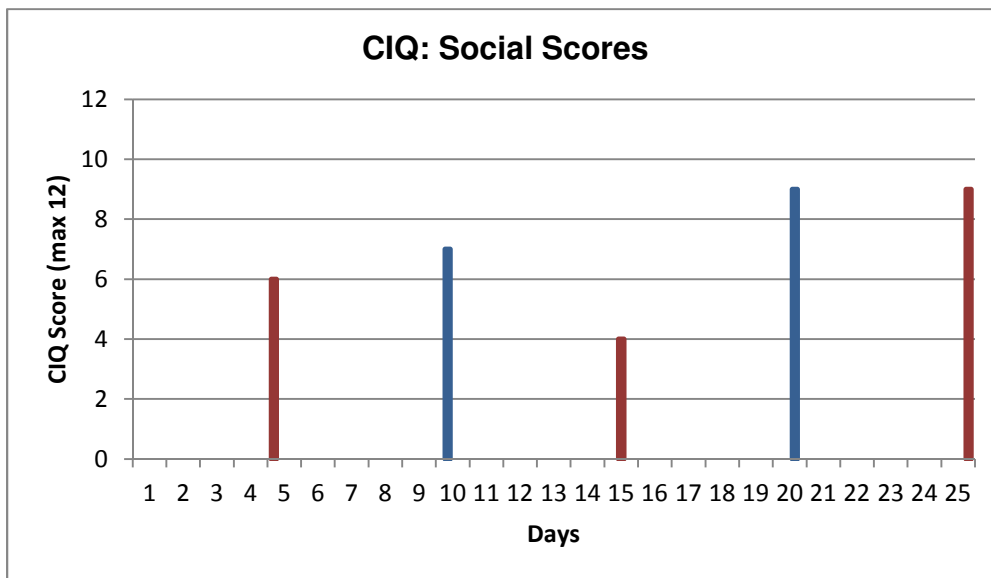


The CIQ and POPS assessments were included largely to determine change over the longitudinal portion of the study, should the participants decide to continue using the PoNS™ device. The graphs of the CIQ are shown and described here. However, it must be acknowledged that the time between each assessment was only one week. It would be very difficult for the participant to experience a true change in the level of community integration in one week. The participant's CIQ scores were plotted as total scores for the assessment, and as Home, Social and Productive Subsection.

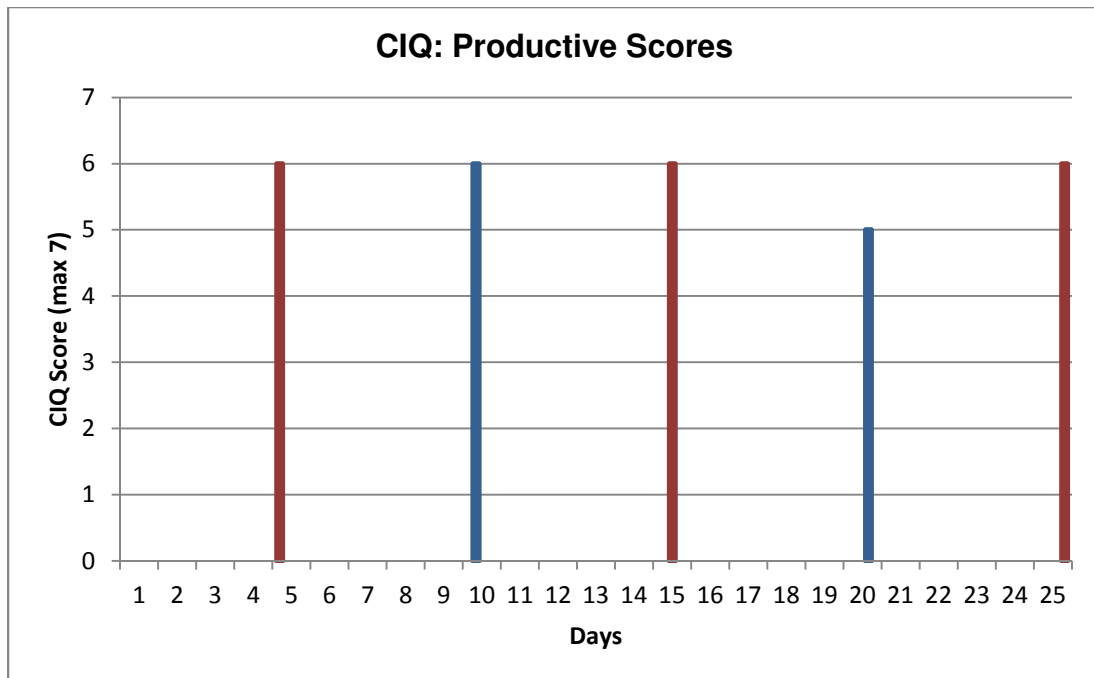
The maximum score on the CIQ is 29 points. The participant's CIQ total score increased one point after the first intervention week, decreased three points after the first withdrawal week, increased four points after the second intervention week and increased one more point after the second withdrawal week.



The maximum score on the Home subsection is 10 points. The participant had the maximum score on the home subsection of the CIQ after each phase.



The maximum score for the Social subsection is 12 points. The participant's scores on the social subsection varied the most of the subsections. The participant's score increased by one point after the first intervention week, decreased three points after the first withdrawal week, increased five points after the second intervention week and remained at that level after the second withdrawal week.



The maximum score on the Productive subsection is 7 points. The participant's scores were constant the first three weeks of the study, decreased one point after the second intervention week, and increased one point after the second withdrawal week.

Appendix D: Research Proposal

Introduction

The brain is constantly interpreting information, making and strengthening connections, and can restructure itself, to some degree, to meet these needs most effectively. This ability to change and mold is referred to as neuroplasticity. In the event of brain trauma and injury, the brain is able to adapt to some impairments, particularly with beneficial interventions and training. Neurorehabilitation capitalizes on the brain's ability to restructure and relearn information for individuals with neurotrauma; most commonly treated are individuals with strokes, traumatic brain injuries and spinal cord injuries. Neurorehabilitation focuses on reinforcing, creating and continuing neuroplasticity using various intervention theories and techniques. However, impairments from each of these diagnoses are often long lasting or permanent and the impairments decrease the individual's functional abilities, even after rehabilitation services are completed.

Neuromodulation, a related field of study, uses electricity or medications to alter the nervous system. Unlike neuroplasticity, this may not be equated to learning, rather the interventions either suppress or enhance the nervous system. While neuroplasticity is a restructuring or reorganization, neuromodulation effects can be dependent on the intervention being present; without the intervention, the effects are eliminated. Many neuromodulation interventions are invasive and costly and results are not permanent without the medication or electricity.

A new neuromodulation intervention called Cranial Nerve Non-Invasive NeuroModulation (CN-NINM) provides a promising intervention for

neuromodulation in various impairments. It was created based on observational results from sensory substitution interventions and the biofeedback device called BrainPort™. Each of these will be described briefly in the context of information learned for the development of the CN-NINM intervention. It eliminates the risks associated with an invasive or implanted device and has shown promise for improving a wide range of impairments that remained after standard rehabilitation. In comparison to existing interventions, the CN-NINM intervention is less expensive, has shown positive results in several patient populations, and may require less time from medical professionals. Although the intervention has shown great promise for improving various abilities, no research has documented the withdrawal effects or carryover. This is a critical branch of research to understanding how the intervention works and how it may be best used as a clinical tool.

Due to the nature of the injury and exploratory results found with the CN-NINM intervention, this study will test the withdrawal effects on individuals with past traumatic brain injuries (TBIs) who have a functional gait impairment. A TBI population was selected because the impairment is in a more centralized location; the brain is impaired but the periphery nerves have not been damaged. Observational results of past CN-NINM use have indicated that individuals with traumatic brain injuries respond well and quickly to the intervention, making it feasible and ideal for a single subject withdrawal study.

Neuroplasticity

Although neuroplasticity occurs automatically, advances in science have led to better understandings of it and how it could be facilitated and utilized. Coined in the 1940's, neuroplasticity refers to the nervous system's ability to respond to stimuli by reorganizing its structure, function, and connections by modifying, strengthening, creating, and eliminating synaptic connections (Cramer et al., 2011; DeFina et al., 2009). In addition to changes in neural pathways and synapses, neuroplasticity can also be from neurochemical, synaptic, receptor, and neuronal changes (Bach-y-Rita & Kerckel, 2003). Neuroplasticity occurs due to habituation, learning and memory, and cellular recovery after injury (Stehno-Bittel, 2002). According to Cramer et al. (2011), neuroplasticity can occur "during development, in response to the environment, in support of learning, in response to disease, or in relation to therapy". It is a natural process, occurring, to some degree, automatically given appropriate environments. Once thought to cease as people aged, neuroplasticity is now known to occur throughout the lifespan. Research supports, however, that the brain appears most plastic at a young age. This can be demonstrated by the success in surgeries such as hemispherectomies, which are most successful in children under age six for regaining normal function, or comparative success of cochlear implants in children under three and a half (Cramer et al., 2011).

Although it can occur automatically and across the lifespan in normal development, many factors can influence the brain's plasticity. Some factors cannot be controlled or manipulated. For example, neuroplasticity may gradually

decrease with age (Dimyan & Cohen, 2011). After an injury or damage to the brain, the length of time since the injury can influence neuroplasticity. Motivation and attention, partially controllable variables, greatly impact neuroplasticity. Although the brain is capable of reorganization, it acts most effectively when the individual is motivated to complete a task, master an objective, or closely attuned to the stimulus. Other variables can be and often are manipulated to produce desired effects. The most commonly manipulated variable to increase neuroplasticity is repetition. Repetition can cause restructuring of the central nervous system, and is often a primary component of interventions used in rehabilitation as discussed later. The repetition should also be experience or task specific; repeating a task will increase the ability to complete that task, but may not transfer to a similar task as effectively. Increased exposure to and repetition of information causes a refining of the neural pathways, thus making the paths more efficient. Pharmacotherapies can be used to facilitate neuroplasticity after an injury or impairment. The best results with pharmacotherapies occur when coupled with targeted interventions or behavioral reinforcement. When attempting to increase neuroplasticity, almost all interventions include a great deal of repetition and a focus on completing functional tasks as opposed to fractured components of a task (Cramer et al., 2011; Dimyan & Cohen, 2011; O'Malley, Ro, & Levin, 2006).

In addition to natural reorganizing due to the environment and common stimuli or regaining function lost after a trauma, neuroplasticity can be used to train the brain to interpret novel information in a specific manner. Possible

because of the ability to reorganize and restructure, the intention of training the brain to interpret information in a specific manner is not always to relearn skills previously mastered but rather to process information presented in a different format. Sensory substitution and biofeedback measures are specific examples detailed below of using neuroplasticity for learning information presented in a different format.

Sensory Substitution

A current research area exploring the uses and benefits of neuroplasticity is the use of sensory substitution. In this approach, individuals with a sensory impairment are provided equivalent information in a different format. There are many forms of sensory substitution. Reading Braille uses sensory substitution; visual information is provided and interpreted through a tactile medium, similarly to that of a cane used by individuals with visual impairments (Bach-y-Rita & Kercel, 2003). The brain only receives information via electrical impulses; it cannot “see” or “feel” items for example, rather, it interprets electrical signals into the perception of the sensation. This simple premise is the basis for sensory substitution. When there is an impairment in the transmission of information, it is theoretically possible to be able to use the sense again, were the electric signal able to bypass the impairment. For example, individuals who are blind may be unable to see secondary to an impairment within the eye structure. If the electrical impulses from the impaired eye could reach the brain, the brain could interpret the information and the individual would have the perception of seeing. Sensory substitution attempts to circumvent the impairment and provide electrical

impulses to the brain that can be practiced and learned to be interpreted as information from the impaired sense (Ptito, Moesgaard, Gjedde, & Kupers, 2005).

Previous research with sensory substitution has explored the use of various means of information input, such as patterns of tactile pressure, audio information, or small amounts of electrical stimulation. Electrical stimulation has become one of the most widely used form of sensory substitution (Ptito et al., 2005). Studies have attempted to provide stimulation to the hands, forehead, abdomen, and tongue, with the best overall results occurring from electrical stimulation to the tongue. The individual, with training and practice, is able to adapt and interpret the information similarly as when information came from the original source. This process ultimately modifies the nervous system and is only possible due to neuroplasticity (Bach-y-Rita & Kercel, 2003; Lozano, Kaczmarek, & Santello, 2009; Tyler, Braun, & Danilov, 2009).

Research from sensory substitution indicates the tongue is an optimal location to provide input and stimulation for multiple reasons. The mouth provides a secure, discreet, and isolated environment for the stimulation. Unlike the abdomen, hands, and forehead which are influenced by the outside environment, the mouth maintains a relatively constant temperature and typically is not stimulated by things like a breeze whereas the skin readily picks up environmental stimuli. Saliva's composition makes it a useful component in the provision of electrical information because it maintains a constant pH+. Saliva also reduces the stimulation required for perception and interpretation. When electrical stimulation is provided on the skin, it must reach a threshold perceptible

to the individual. This varies based on location of nerve receptors, requiring less in the fingers than on the abdomen, but the tongue requires less stimuli to respond than even the fingers. The tongue and mouth are very sensitive to information yet capable of interpreting a great deal of information. In addition to the benefits of using the tongue, research has not indicated negative effects or negative perceptions of providing electrical stimulation to the tongue. The intensity required for interpretation is not near the pain level, and patients generally have not described the experience as unpleasant (Fabien, Nicolas, Orliaguet, & Payan, 2007; Kaczmarek, 2011; Vuillerme & Cuisinier, 2009; Wildenberg, Tyler, Danilov, Kaczmarek, & Meyerand, 2010).

Sensory substitution research has provided a solid foundation and support for the use of therapeutic electrical stimulation of the tongue. Not only has the research been successful in training participants to interpret the stimuli, little to no negative effects have been documented as a result of providing stimulation of the tongue. Observational results during sensory substitution studies have led researchers to believe tongue stimulation could be beneficial in additional areas beyond object recognition.

BrainPort™: A Biofeedback Approach

According to Vuillerme et al. (Vuillerme, et al., 2008), biofeedback provides individuals with “additional artificial information about body orientation and motion to substitute or supplement the natural visual, somatosensory and vestibular sensory cues”. Biofeedback can provide positioning information using visual or proprioceptive cues, and increase body awareness. A Cochrane review

from 2004 found that visual and auditory feedback did not improve functional balance (Badke, Sherman, Boyne, Page, & Dunning, 2011).

The BrainPort™ device was created for individuals with balance impairments to provide real-time cues on head positioning (Badke et al., 2011). It contains an accelerometer, and when movement from the center is detected, the BrainPort™ transmits the signal to electrotactile stimulation of the tongue. For example, if the head moves/leans to the right, the electrotactile stimulus will be felt on the right side of the tongue (Danilov, Tyler, Skinner, Hogle, & Bach-y-Rita, 2007).

This device has been used with populations with chronic balance dysfunction due to peripheral or central etiologies (Danilov et al., 2007), stroke (Badke et al., 2011), and healthy populations with vision occluded (Vuillerme & Cuisinier, 2009). After the initial time required to learn how the device works and what each condition felt like, each population tested was able to successfully improve balance scores after using the BrainPort™ device.

A 2009 study (Vuillerme & Cuisinier, 2009) used nine healthy young males with no vision or balance impairments. When tested without feedback from the BrainPort™, participants had significant differences in head displacement scores when vision was available than when it was not. When feedback from the BrainPort™ was provided, there were no differences noted depending on the vision condition. Testing was completed after practice trials to become familiar with the device. The order of presentation of conditions was randomized for

participants. There were no mentions of participants feeling uncomfortable with or disliking the stimulus (Vuillerme & Cuisinier, 2009).

A 2011 study on the effects of an 8-week intervention with BrainPort™ on 29 individuals post-rehabilitation following a stroke found clinically significant results for most participants on some combination of assessments. Although numerous assessments and results were reported, only a brief summary designed to show the magnitude of clinically significant findings are reported here. Participants were tested on five assessments. Of these assessments, 27 of 29 participants improved more than the minimal clinically important difference (MCID) on at least one assessment and 3 participants improved more than the MCID on all five assessments. Two participants' scores decreased more than the MDIC, one on the Timed Up and Go, and the other on the Stoke Impact Scale – Mobility score. Overall improvements showed great promise for the vast majority of the population studied (Badke et al., 2011).

A 2007 study's population included 28 individuals with many types of chronic balance dysfunction. Participants were post-rehabilitation, and used the BrainPort™ device for 3-4½ days. Observational results report all participants with impaired gait had notably improved gait. All participants reported improvements in balance-challenging tasks, and all participants improved on the SOT with an average improvement of 42% (Danilov et al., 2007).

Overall, the BrainPort™ has demonstrated significant improvements in balance for various population groups and the effects were noted to have some carryover. However, methodologically strong studies have not been completed

and a great deal more research on this topic is needed. No formal documentation of withdrawal effects was indicated. Some descriptive information from involved authors indicates additional benefits aside from anticipated balance improvements. Although uncertain as to the rationale or physiology of the changes, participants reported improved quality of life (Badke et al., 2011), balance, gait, sleep, concentration, coordination, multitasking, and mood. These findings, in part, led to the design and exploration of the CN-NINM intervention (Tactile Communication & Neurorehabilitation Laboratory, 2007).

Neurorehabilitation

The brain's ability to relearn and restructure has led to the growing field of neurorehabilitation, which aims to increase function and reduce impairments caused by a neurotrauma. Neurorehabilitation can benefit individuals with a multitude of injuries, and neurotraumas can include any trauma to the nervous system, however the primary diagnoses treated in these fields are stroke, traumatic brain injury, and spinal cord injury. Since the brain is the body's control center, injury to the brain could cause any number of countless impairments and depend on the location and cause of injury. Most individuals with traumatic brain injuries or strokes have motor impairments along with potential cognitive and psychosocial impairments. Many medical facilities have neurorehabilitation specialists, as treatment approaches and interventions may vary from other specialty areas. Primary members of the rehabilitation component of the team include both physical and occupational therapists. Both therapists aim to increase functioning of the patient, facilitate relearning, and increase mastery of

skills to help return patients to their prior level of functioning (American Society of Neurorehabilitation, 2012).

Neurorehabilitation specialists can use a wide variety of interventions to facilitate neuro-reeducation and neuroplasticity, both traditional and innovative. Neuro-reeducation is the primary intervention objective and attempts to succeed in relearning tasks. Techniques used in conventional neurorehabilitation can include gait training, aerobic training, biofeedback, and, increasing in popularity, the use of robotic or robot-assisted therapies. All the listed interventions utilize a great deal of repetition to be successful, and all require a learning period, significant practice and time to see results. In addition, they typically are completed under the observation of a rehabilitation specialist such as an occupational or physical therapist. Innovative intervention ideas for neurorehabilitation include the use of neuroprostheses and devices for neuromodulation such as pharmacological approaches, invasive, or non-invasive electrical stimulation, as described in more detail below (Cramer et al., 2011; Dimyan & Cohen, 2011; O'Malley et al., 2006).

Neuromodulation

Neuromodulation is the therapeutic alteration of the nervous system, either pharmacologically or electrically. It can be used to enhance or suppress electrical activity in any section of the nervous system. Examples include baclofen pumps, spinal cord stimulators, deep brain stimulators, and transcranial magnetic stimulation. These interventions have begun to gain more widespread acceptance and have positive results, but many are invasive procedures that

require a highly trained surgeon and specialist, have a risk of complications, and are ultimately costly. New interventions are exploring the use of non-invasive techniques; one in particular is called Cranial Nerve Non-Invasive NeuroModulation (CN-NINM). Three neuromodulation techniques will be briefly explored and compared.

Electricity has been intentionally introduced to the brain and body to study the effects since the 1870s. Initially used to help map function and identify structures, it was not until the 1960's that the idea of using electrical stimulation as a therapeutic intervention began to emerge. This novel idea was perpetuated by documentation of positive phenomena that occurred from brain stimulation, such as a reduction in tremors for individuals with Parkinson's Disease (Perlmutter & Mink, 2006).

Deep Brain Stimulators

Deep brain stimulators are a type of neuromodulator that use electrical stimulation to alter the nervous system. Although not used until the 1990's, deep brain stimulators (DBS) have quickly gained favor in the medical community. DBS consist of an electrode surgically implanted into the brain with a wire connector to a pulse generator device surgically implanted under the clavicle. The electrode can be implanted numerous locations in the brain, depending on the reason for the device and effects noted during the surgical insertion. The most common use of DBS is to alleviate Parkinson's Disease symptoms, particularly tremors. Research has not indicated that the device has any effect on disease prognosis; rather, it is intended to reduce or eliminate symptoms to

increase the individual's functional abilities while receiving the stimulation. The DBS device located below the clavicle can be adjusted to different intensities based on symptoms, and can be turned off and on, and fine-tuned over time. The effects of the DBS can be almost immediate; turning off the device allows a return of the symptoms, like tremor from Parkinson's Disease, within seconds through several hours for other symptoms such as freezing gait (Kern & Kumar, 2007).

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) also uses electrical stimulation for neuromodulation, but is a non-invasive approach. It utilizes a stimulating coil, held directly next to the head, to send an electrical impulse into the brain. This stimulation however can only influence the surface of the brain because the intensity of the stimulation decreases very quickly in relation to the distance from the coil. Depending on the type of stimulation provided, effects of the stimulation can be a decrease in brain stimulation in the area, an increase in stimulation, and, when using repetitive TMS, the effects may have some type of carryover. O'Malley, Ro, and Levin (2006) report that using the repetitive TMS for 15 minutes can decrease the cortical excitability for up to 15 minutes. Individuals after a stroke often have decreased cortical excitability on the hemisphere of the incident, and increased excitability on the contralateral hemisphere. Because changing the frequencies of the stimulation change whether the effects of the TMS are generally excitatory or inhibitory, TMS may be beneficial to some individuals with a stroke, depending in what part of the brain the incident

occurred. TMS has also been used to stimulate the prefrontal cortex to reduce depression. With each of the interventions TMS is used for, targeting training activities are very important to promote relearning along with the neuromodulation. Overall, although promising particularly in stroke intervention, TMS may be limited due to the difficulty with providing stimulation to an exact brain location, limited area of the brain affected, and unknown lasting effects (Cramer et al., 2011; O'Malley et al., 2006).

Cranial Nerve Non-Invasive NeuroModulation (CN-NINM)

The CN-NINM intervention was established after repeated observations made while completing sensory substitution and electrical biofeedback balance research with the BrainPort™. Some of the common effects noted in multiple patients were improved balance, gait, sleep, concentration, coordination, multitasking, and mood (Tactile Communication & Neurorehabilitation Laboratory, 2011). After working closely with other neuromodulation and neuroplasticity concepts and research, a team of researchers at the Tactile Communication and Neurorehabilitation Laboratory (TCNL) created a device with features based on the BrainPort™ device. However, unlike the other interventions that use electrical stimulation, the CN-NINM couples individualized targeted training activities with information-free stimulation to the tongue as opposed to providing information specific to a component of the environment that must be interpreted (Wildenberg, Tyler, Danilov, Kaczmarek, & Meyerand, 2010, 2011). As mentioned previously, completing activity-specific interventions while providing neuromodulation or increasing neuroplasticity is important to increase

the relearning and efficiency of desired activities (Cramer et al., 2011; Dimyan & Cohen, 2011; O'Malley et al., 2006).

The CN-NINM intervention consists of two primary components, electrical stimulation of the tongue using a Portable Neuromodulation Stimulator (PoNS™) device, paired with targeted training activities, which vary based on diagnosis and what impairment is being studied. Protocols for the intervention have been established, each customized slightly depending on diagnoses and targeted impairments (See Appendix 2 for a sample protocol for a previous MS study). For example, fatigue is a common concern for patients with Multiple Sclerosis, so more options for rest periods were integrated into the protocol, depending on energy levels, whereas populations with central balance impairments followed a more routine intervention. Each component of the CN-NINM intervention is described in greater detail, followed by an overview of the literature regarding CN-NINM and decision to study a population with traumatic brain injury on withdrawal effects.

Portable Neuromodulation Stimulator (PoNS™) device

Research on and work with the predicate BrainPort™ device led to the design and basis for the PoNS™ device currently used in CN-NINM interventions. This device continues to use the tongue as the stimulation receptor for the reasons indicated previously. In addition to the protected, electrically beneficial environment, and sensitivity of the tongue, the tongue also provides access to branches of two cranial nerves, the Lingual nerve, part of the trigeminal nerve (CN V) and the Chorda tympani, part of the facial nerve (CN VII). The

activation and excitation of both cranial nerves as well as the great number of other nerves in the mouth and tongue provide comparatively direct connections to the central nervous system compared to previously studied human interface locations (Tyler, Braun, & Danilov, 2009; Wildenberg et al., 2011)

The PoNS™ device is a T-shaped, battery powered, portable device. The oral tab that provides the stimulation is 32mm wide and .84mm thick, and the device case measures 68mm wide, 45mm long, and 15mm thick (see Figure 1). When recharging, the charging circuitry and power connector are designed to prevent device use, thereby eliminating the possibility of electrical shock while charging.

Figure 1: The PoNS™ device



When in use, the PoNS™ device delivers 5 ms of stimulation every 20 ms. The voltage and pulse timing for each device are established and not able to be altered, however, device users can adjust the pulse-width to alter the intensity by pressing either the “Decrease Intensity” or “Increase Intensity” buttons on the device. Each time the device is turned on the intensity starts at the lowest level (.4Us) and can be adjusted up to 60Us, the highest intensity possible. The device has a maximum of 19 V and 6 mA. The PoNS™ device consists of 16 electrodes, of which only one is active, and the rest ground the stimulation to minimize the potential for negative side effects. The amount of stimulation used is described

as feeling like drinking a carbonated beverage and should not be a noxious stimulus (Wildenberg et al., 2011). The PoNS™ device is recognized as a nonsignificant risk (NSR) device by the Food and Drug Administration (See Appendix 3 for a copy of the FDA NSR designation). At the current time, it has not yet received FDA approval. To date, there have not been any documented negative effects as a result of the use of the PoNS™ device or the BrainPort™. Similar intervention stimulus used in sensory substitution similarly does not indicate negative side effects when using electrical stimulation of the tongue. (For more specific information regarding the PoNS™ device, see Appendix 1.)

The results of the CN-NINM intervention are believed to be caused by a large influx of tongue stimulation, stimulating the brainstem and cerebellum through the cranial nerve tracts. Additional research needs to be completed to confirm or correct inconsistencies in this theory. This significant activation proceeds through other interneuron circuitry as well as through direct collateral connections. This stimulation is believed to “prime” the brain for learning activities, thus justifying the use of targeted training activities in addition to the stimulation (Wildenberg et al., 2010, 2011).

A 2011 study by Wildenberg et al. used fMRI to discover how the brain was affected by the CN-NINM with balance training. Nine participants with chronic balance dysfunction underwent fMRIs before and after 19 sessions of stimulation, each 20 minutes long and paired with standing balance activities with feet together and eyes closed. Seven of the nine participants had improved sensory organization testing (SOT) scores, with an average improvement of

15.75 points (SE=5.59, $p=.026$, paired Student's t-test), possible SOT scores range from 0-100. High resolution scans showed activations of optic flow in the right vestibular nucleus and right superior colliculus as well as multiple cerebellar structures. After CN-NINM, the right trigeminal nucleus, the site of origin for the neuromodulation in behavioral and subjective measures improvement, showed increased response to optic flow. This supports the idea that the neuromodulation is task dependent (Wildenberg et al., 2011). After prolonged activation, the circuits can undergo neuronal reorganization, thus leading to an increased ability to learn or relearn tasks and demonstrating the plasticity of the brain.

Targeted Training Activities

The stimulation from the PoNS™ device is believed to prime the central nervous system for learning. Thus, it is important to pair the stimulation received with personalized, appropriately challenged activities, specific to the impairment targeted. If the intended goal is improved gait, targeted training on gait tasks should be included while using the PoNS™ device for best results. The targeted training activities are completed at a maximal challenge level for participants so they are difficult but not impossible tasks. Targeted training activities can be very difficult and require a great deal of motivation from the participant. Because of the specialization, they also require a learning period where the interventions occur under the supervision of a trained researcher (see Procedures for additional information regarding the researcher training prior to patient contact). Once the patient is competent in the intervention, depending on the type and

length of study, it may be possible to allow them to continue the interventions at home independently. Although the stimulation facilitates learning, the targeted training is important to focus the primed nervous system to learn the intended task or activity (Tactile Communication & Neurorehabilitation Laboratory, 2011).

Initial CN-NINM Research

The TCNL team initially began research using the CN-NINM intervention on populations with balance impairments and disorders. Targeted training therapeutic activities while using the PoNS™ device included trainings on balance, gait, and relaxation. Individuals with balance impairments showed a decrease in overall sway and sway in response to optic flow after one week of CN-NINM training as detected on fMRIs. After the week of CN-NINM, there was no longer a significant difference noted between controls and participants in optic flow. Changes in balance and gait after the CN-NINM intervention are believed to have some carry-over since the participants were not tested while using the PoNS™ device (Wildenberg et al., 2010, 2011). This is in contrast to most electrical neurostimulation, like deep brain stimulators, which are believed to only produce behavioral effects when active or very shortly thereafter. Research specific to exploring the carry-over or withdrawal was not found.

Recent CN-NINM research.

In 2011, Danilov, et al., studied the balance and gait effects of neuromodulation on individuals with multiple sclerosis (MS) using the CN-NINM intervention. Twenty participants with MS completed a 14-week protocol and after a 2-week in-laboratory training were provided a PoNS™ device to use at

home. Results found that individuals in the active group who had completed the CN-NINM training improved in functional gait as measured by the DGI more quickly than the control group and reached twice the improvement of the control group by the end of the first two weeks. At the 10- and 14-week assessments, this difference was highly statistically significant. The only difference between group demographics was found to be number of years with MS; the greater the length of time since diagnosis with MS typically reflects poorer functioning. In this study, although the active group generally had a longer time since diagnosis, they improved on the Dynamic Gait Index at a faster rate than the control group. Statistically significant differences on the SOT were not found (Danilov, Tyler, Rust, Kaczmarek, & Subbotin, N. D.).

Overall Quality of Research Available on CN-NINM Intervention

Although there is relatively little published on the effects of CN-NINM, over 300 participants have been studied across multiple impairment categories using the BrainPort™ and PoNS™ devices (Dr. Yuri Danilov & Kathy Rust, personal communication). These participants have provided and continue to provide qualitative and quantitative information and results that have helped create and improve the protocols used for future research. Research has indicated that a rigorous training protocol, paired with electrical stimulation, may slow or improve certain aspects of function for impairments that are systemic and progressive such as MS (Danilov et al., N.D.). Research has also demonstrated favorable results for individuals with various sorts of central and peripheral balance impairments. Impairments that are progressive and neurodegenerative may take

longer to show effects or show a slowing of progression, whereas individuals with impairments secondary to a brain injury likely show faster and more significant improvement due to the nature of the injuries. In observational research completed at TCNL with individuals with a brain injury, effects of the CN-NINM intervention showed tremendous results very quickly upon beginning the intervention (personal communications).

Traumatic Brain Injuries

Traumatic Brain Injuries (TBIs) are a significant and growing public health problem defined as any injury that “disrupts the normal function of the brain” (CDC, 2012). Each year at least 1.7 million people in the United States are affected by a TBI (CDC, 2010). TBIs can vary in intensity, and are classified as either mild, moderate or severe. Young adult males and elderly populations are the two groups most likely to sustain a TBI. Due to the recent wars and increased military actions, more soldiers are being diagnosed with brain injuries; from 2000-2011, 220,000 service members were diagnosed with a TBI (Pellerin, 2012).

TBIs can result in lasting functional impairments. The combination of impairments often experienced by an individual after a TBI increases the risk of falls, which can lead to reinjury, other injuries, and amplification of symptoms (CDC, N.D.). The increased risk comes from impairments in balance and gait, as well as increased impulsivity, decreased problem solving and a reduction in the ability to multitask, whether the multitasking involves physical tasks (carrying something while walking) or cognitive demands (answering a question or being distracted by something) (CDC, N.D.; Dijkers, 2004; Kashluba, Hanks, Casey, &

Millis, 2008; McCulloch, Buxton, Hackey, & Lowers, 2010; McFadyen et al., 2009; Rezai & Corrigan, N.D.). Gait impairments after a moderate and severe TBI are a common complaint (Basford et al., 2003; McFadyen et al., 2009; Williams, Morris, Schache, & McCrory, 2009).

It is common for a primary rehabilitation focus to be regaining ambulation, if possible (McFadyen et al., 2009; Williams et al., 2009). Independent mobility requires a great deal of skills aside from strictly physical abilities. For example, mobility requires the coordination of various systems, the ability to process sensory information, the ability to navigate in the environment and back to the intended destination, and being aware of the surroundings. Independent mobility can often provide the individual with control and a great deal of improvement in multiple domains (McFadyen et al., 2009). Because of this, impairments in balance and gait can lead to decreased independence, physical fitness, community participation, and quality of life, and an increased risk of falls and reinjury (Betker, Szturm, Moussavi, & Nett, 2006). However, the ability to walk does not imply the individual does not have gait impairments that will decrease function and independence since high-level gait activities are often necessary, such as picking something up from the floor while walking, or turning his/her head while walking. These impairments, compounded by the additional long-term impairments that may be present like impulsivity and poor problem solving, may decrease the independent functional ability and community integration of an individual with a TBI long after he/she is physically able to ambulate in the community or increase the risk of reinjury (CDC, N.D.).

Connection of TBI to CN-NINM

The proposed study will use a population of individuals who have had a traumatic brain injury. TBIs will be recruited for several reasons. First, individuals with TBIs often have a high level mobility impairment. Although able to live in the community, they may have difficulty completing tasks such as walking in a crowd or turning their head while walking. The CN-NINM has been used previously for balance and gait impairments. This study will provide additional information for a protocol very similar to the protocol used previously. Second, one of the two most affected age groups is young adult males. The proposed study will be excluding participants if they are over the age of 65 to reduce confounding variables of natural decrements in balance with age. Young individuals with a static gait impairment will likely have to compensate for the impairment all of his/her life, which may end up detrimental for independence and functioning, overall medical costs, and psychosocial adjustments. Third, the proposed study will begin to document the withdrawal effect of the CN-NINM intervention. To keep the study feasible and practical it is necessary be able to see results quickly. Previous patients with TBI have responded quickly to the CN-NINM intervention (personal communication). By using participants with TBI, the study will be able to study two intervention periods and two withdrawal periods per participant, thus strengthening the design of the study.

Significance to Occupational Therapy

Occupational therapists are a primary rehabilitation provider in neurorehabilitation, a field that works primarily with TBI, spinal cord injury, and

stroke. Many patients after a traumatic brain injury have lasting impairments when they return to the community, including balance and gait impairments; this increases the cost of care for that individual if they are not independent. A reliance on other people for assistance can also decrease self-confidence. Occupational therapists often work in rehabilitation to improve functional abilities and functional mobility. Functional mobility is critical for being able to complete self-cares, for completing Instrumental Activities of Daily Living (IADLs), and often for obtaining and maintaining leisure and work activities. Impairments in these domains can cause a decrease in community integration and feelings of confidence. A lack of community integration can increase isolation and decrease independence. Occupational therapists attempt to speak to all of these needs, addressing physical, emotional, and psychosocial domains. Improving high level functioning may increase community participation, confidence completing gait activities, and independence. This intervention particularly shows significant promise in rehabilitation due to its relative inexpense, ease of use, and lack of complete dependence on trained rehabilitation professionals to achieve significant gains.

Hypotheses

1. During each of the two, 5-day CN-NINM intervention phases, participants' gait performance scores will significantly increase when compared to their baseline scores (as measured by the Community Balance & Mobility Scale).
2. During each of the two, 5-day CN-NINM intervention phases, participants' confidence in gait activities will significantly increase when compared to their

- baseline confidence scores (as measured by the modified Gait Efficacy Scale).
3. During each of the two, 5-day withdrawal phases, participants' functional gait performance will show a decrease in function until reaching baseline function (as measured by the Community Balance and Mobility Scale).
 4. During each of the two, 5-day withdrawal phases, participants' confidence in gait activities will show a slight decreasing trend but will not reach previous baseline levels (as measured by the modified Gait Efficacy Scale).

Methods

Research Design

This study used a single subject experimental design with five data points collected in each phase. The participant followed an A-B-A-B-A design. 'A' indicates a baseline phase with no intervention and the two subsequent 'A' phases are withdrawal phases with no intervention. 'B' indicates the CN-NINM intervention. Each phase lasted one week, with participants completing the protocol Monday through Friday. No interventions were completed on the weekends. One week interventions were chosen based on previous laboratory observations from a researcher and clinician trained in the CN-NINM intervention and gait assessments.

Variables

The independent variable in this study is the CN-NINM intervention. The intervention is explained in detail in Procedures. The two dependent variables are 1) **quality of functional gait tasks**, as measured by the Timed Up and Go, Romberg and Sharpened Romberg and components of the Community Balance & Mobility Scale and Dynamic Gait Index, and 2) **confidence completing common gait tasks**, as measured by a modified version of the Gait Efficacy Scale.

Participants

One community dwelling participant with a closed TBI completed the study. The study had extensive inclusion and exclusion criteria to provide the best chance of the intervention being appropriate and participants showing

results in a short period of time. Extensive criteria also ensured all participants were sufficiently similar so they might react similarly to the intervention.

Inclusion Criteria

Participants must:

- be between the ages of 18-65
- speak English fluently
- must be their own legal guardian, be able to understand and give informed consent
- have a clinically detectable gait impairment secondary to a closed traumatic brain injury
- live in the community
- no longer be receiving rehabilitation or balance training programs of any kind
- be able to maintain upright posture for 20 minutes
- be able to ambulate 10 meters without resting with or without assistive devices
- must indicate gait is an impairment they hope to improve

Exclusion Criteria

Participants will be excluded from the current study if they:

- | | |
|---|--|
| <ul style="list-style-type: none"> • have electrical devices/implants such as pacemakers • have a biomechanical prosthetic • have a comorbid diagnosis that could affect balance such as | <ul style="list-style-type: none"> • Multiple Sclerosis or Parkinson's Disease • are pregnant or trying to become pregnant • use tobacco products |
|---|--|

- have contagious mouth diseases, sores, piercings or abrasions
- have tongue neuropathies
- have receptive aphasia
- have uncontrolled pain
- have uncontrolled mental health conditions
- have a history of seizures
- have vision below 20/40
- have myasthenia gravis
- have Charcot-Marie tooth disease
- have post-polio
- have guillan barre
- have fibromyalgia
- have hypertension
- have diabetes
- have chronic fatigue syndrome
- are on medications and have had a major change in type or dosage within three months of enrollment
- lack the motivation necessary to complete the tasks
- lack the cognition to understand and complete the protocols as directed

The participant who completed the study was 35 years post injury. His injury was caused by a motor vehicle accident and resulted in a severe head injury and multiple orthopedic injuries. As a result, the participant used an AFO on his left lower extremity, had a metal plate for support in his right shoe, and used a cane on occasion when he felt unstable or was walking long distances.

Instrumentation

Phone Screening

The phone screening consisted of basic demographic information, background on impairment, and a brief overall impairment list to determine appropriateness for the study. (See Appendix 4 for the phone screening in its entirety.)

Community Balance and Mobility Scale

The primary measure used to evaluate participants is the Community Balance and Mobility (CB&M) Scale. Created in 2002, this tool assesses the function of higher functioning populations of individuals with previous traumatic brain injuries. The 13 tasks assess multitasking, sequencing of movement components, and complex motor skills. Eight of the 13 tasks are timed, as gait impairments can manifest as increased time and caution used to complete tasks; using timed tasks can increase sensitivity to detect these impairments. (See Appendix 5 for the assessment in its entirety.) The CB&M Scale requires approximately half an hour to complete and uses an eight-meter track. Participants are scored on a 0-5 scale with 0 indicating a complete inability to complete task, and 5 indicating the most successful completion of the task (Howe, Inness, Venturini, Williams, & Verrier, 2006).

As described earlier, functional mobility can influence community involvement and independence with tasks. Aware of this during the creation and validation of the CB&M Scale, the authors collected Community Integration Scores throughout their research. Using the results of 47 participants, researchers found an association between the CB&M Scale and Community Integration Scores ($r=0.54$, $p<0.001$). Individuals with a CB&M Scale score of less than 45 (out of a possible 65) had lower scores on the Community Integration Measure. A score of 45 is an appropriate threshold for decreased community participation and integration (Howe, Inness, & Wright, 2011)(Howe, Inness, & Wright, 2011).

The minimal detectable change indicated for the CB&M Scale is 8 points. This will be used as a determinant in the proposed study of true change that is not caused by measurement error. The minimal detectable change was determined using a 90% confidence interval (Howe et al., 2011)(Howe et al., 2011).

Although not extensively documented, the reliability and validity of the CB&M Scale are overall high. The CB&M Scale has high reliability for intra-, inter- and test-retest reliability with intraclass correlation coefficients of 0.977, 0.977, and 0.898-0.975 (for immediate and 5 days later test-retest), respectively. A Cronbach's alpha for internal consistency was 0.96 and 0.95, indicating a high correlation among items. Content validity was assessed in a focus group of physical therapists. All but one task met a priori inclusion criteria. The CB&M Scale appears to have high content validity. Last, construct validity was assessed by comparing it with other related measures. A significant correlation was found with self-paced gait velocity ($r=0.53$, $p=0.001$) and maximal gait velocity ($r=0.64$, $p<0.001$). The CB&M scale has strong validity and reliability when used with a population of individuals with brain injuries (Howe et al., 2006)(Howe et al., 2006).

Protocol Modification

Initially, participants were expected to complete the Community Balance and Mobility Scale as the sole gait measure in the study. On the first day working with the participant, the participant completed all tasks from the study as an exposure round to eliminate a one-time, initial learning effect due to anticipation

of questions and comfort with the assessments. On this day, the participant completed tasks from the CB&M Scale but remarked that several of the tasks caused increased pain (which lasted two full days) and were tasks he avoided at all costs in daily life (such as running, walking and looking horizontally, etc...). Many of the tasks he attempted to complete appeared to be too complex for him to complete. The participant expressed interest in continuing the study if he was able to complete variations of the tasks that did not cause pain. To accommodate his pain-free ability level while obtaining information similar to what would have been acquired, the participant completed components of 4 balance and gait assessments. These included completing the Timed Up and Go, Romberg and Sharpened Romberg, four tasks from the Dynamic Gait Index, and five components of the CB&M Scale.

Due to the inability to use the assessment in its entirety, the reliability and validity of the CB&M Scale and Dynamic Gait Index are no longer possible to be assumed. Data is therefore examined to look for trends and patterns but the scores cannot be standardized or compared to norms.

Timed Up and Go

The Timed Up and Go assesses a participant's mobility and speed rising from a chair. The primary researcher recorded the time to complete the task; qualitative information was not used. Shorter times indicate better performance.

The Timed Up and Go has not been extensively tested for populations with TBIs. A study of children with TBI found excellent test retest reliability (ICC=.86) (Katz-Leurer, Rotem, Lewitus, Keren, & Meyer, 2008). Other studies on

community dwelling adults found cut-off scores to be times below 13.5 seconds for risk of falls (Shumway-Cook, Brauer, & Woollacott, 2000).

Romberg and Sharpened Romberg

The Romberg and Sharpened Romberg assessed the participant's balance with and without vision. Participants complete the Romberg with their feet together and Sharpened Romberg in a tandem stance. The participant has up to three trials to stand for a maximum of 60 seconds in each condition; longer times indicate better performance (Callegari, 2009). The Romberg and Sharpened Romberg have not been normed for TBI. Minimal detectable change scores with a confidence interval of 95% for the Sharpened Romberg with eyes closed ranged from 3-9 seconds and with eyes open ranged from 9-10 seconds. Test retest reliability values (ICC) for volunteers aged 55-75 years old were .72 and .76 for eyes closed and .90 with eyes open (Steffen & Seney, 2008).

Dynamic Gait Index

The DGI assesses functional gait tasks on a 4 point scale (0-3). Higher scores indicate better performance. Four components from the DGI were used for this study. The tasks were: 1) Gait with horizontal head turns, 2) Gait with vertical head turns, 3) Step over an obstacle, and 4) Step around obstacles. Normative data for people in the same age bracket as DS includes a mean score of 23.9 with a range of 22-24 and a standard deviation of 0.4 (Vereeck, Wuyts, Truijen, & Heyning, 2008).

Community Balance and Mobility Scale

The participant was able to complete five components of the CB&MS. These tasks included unilateral stance, tandem walking, crouch and walk, forward to backward walking, and step-ups x 1 step.

Modified Gait Efficacy Scale

The Gait Efficacy Scale was created to assess how confident an individual was in performing select gait tasks. Confidence is an important component to function, as a lack of confidence completing a task will likely lead to a decrease in task performance. A modified Gait Efficacy Scale (mGES), published in 2011, modified the Gait Efficacy Scale to include tasks that were more commonly experienced in daily activities (Newell, VanSwearingen, Hile, Brach, 2012). For the proposed study, the mGES will be further modified to include tasks specifically difficult for individuals after a traumatic brain injury. The assessment used in the proposed study, GES-m, eliminates tasks assessing confidence ascending and descending stairs using a railing, since additional questions remain to assess confidence with these tasks without using a railing. Two additional tasks will be added to assess confidence walking in a crowd and walking through aisles, such as at a grocery store.

Although tested for older adult populations, the GES-m assesses tasks that will likely be affected in the proposed study and tasks that individuals with a traumatic brain injury may find difficult. This assessment demonstrates a low likelihood of a ceiling effect which was an important consideration for the assessment used in the proposed study. The GES-m is a ten item measure that

uses a 1-10 Likert-like rating scale with a 1 indicating no confidence completing the task and a 10 indicating complete confidence completing the task. The GES-m takes approximately five minutes to complete (Newell et al., 2012). See Appendix 6 for the complete assessment.

A change of six points appears to indicate a “true” change in that a change of six points indicates confidence that the score changes reflects a change in confidence (Newell et al., 2012). A six point change will be used in the proposed study to indicate a change in confidence.

The mGES has strong reliability and validity. Test-retest reliability after one month had an intraclass correlation coefficient of 0.93 (CI 0.85-0.97). The Cronbach alpha was 0.94. The mGES correlated strongly with the Activity-specific Balance Confidence assessment ($r=0.88$), Falls Efficacy Scale ($r=-0.80$) and the Late Life Function and Disability Instrument ($r=0.88$) (Newell et al., 2012)(Newell et al., 2012)

Procedures

Completion of the study was completely voluntary, and subjects could withdrawal from the study or choose not to answer any questions at any point without negative consequences. To further strengthen the proposed study and produce as reputable and usable results as possible, guidelines set by Kratochwill et al., in 2010 were used as a guide and reference as much as possible (Kratochwill, Hitchcock, Horner, Levin, Odom, Rindskopf, & Shadish, 2010.)

Researcher Training

The primary researcher for the study received training on the CN-NINM intervention from the Tactile Communication and Neurorehabilitation Laboratory (TCNL) at the University of Wisconsin Madison prior to contact with any potential participants. The training consisted of observation and hands on experience with the device and intervention. Training continued until the primary researcher and expert were confident in the ability of the primary researcher to understand and follow the protocol and apply it to participants.

Phone Screening

Prior to the study, interested participants completed a phone screening. At this time, the study was explained in detail, including a brief background of the intervention, what was expected of the participant, and the study time commitments. Participants were screened to ensure they met inclusion and exclusion criteria. The primary researcher collected basic demographic information and a brief impairment list. The only eligible participant set up a time to begin the study. (See Appendix 4 for the phone screening in its entirety.)

Subjective, free-response journaling

Throughout the study, the participant was encouraged to document his experiences with each phase in the study in an informal, unstructured journal. The information was discussed daily to ensure the participant was following the protocols as directed and address and document any changes he noted.

First Visit

Prior to beginning data collection, the participant received an informed consent approved by the Institutional Review Board at the University of Wisconsin-Milwaukee. The researcher again explained the study and clarified the expectations for the participant. The participant was provided time to read the document and ask any questions prior to signing. After signing the informed consent, the participant completed the self-report surveys, the GES-m, and the CB&M Scale. According to the protocol established, the scores on these measures were thrown out and the day was used as practice and awareness of the assessment components.

While completing several of the CB&M Scale components (running, walking and looking, etc...), the participant experienced pain in his lower back and left lower extremity that persisted approximately 48 hours. After further discussion and prior to beginning the study, the participant expressed an interest in completing the study if he could complete tasks that did not cause pain. The primary researcher chose to include the Timed Up and Go, Romberg and Sharpened Romberg, four components of the Dynamic Gait Index, and five components of the Community Balance and Mobility Scale to incorporate many of the variables addressed in the CB&M Scale at a graded intensity level. The participant agreed to completing the tasks and all were at a level appropriate to the participant's abilities. Due to time and financial constraints, the participants will not be blinded to the study conditions and the study will not employ any sort of randomization.

Week One: Baseline Function

During the first week of the study, the participant was tested once daily in the afternoon, Monday through Friday, under the observation and direction of the primary researcher. The participant completed the balance and gait tasks to establish a baseline for functional gait ability. On Friday, the participant completed the GES-m, POPS, and CIQ to establish a baseline of confidence with gait activities and perceived community integration.

The primary researcher encouraged the participant to complete periodic subjective journal entries to document their experiences throughout the study. The participant made short notes regarding his experience, and the primary researcher and participant discussed changes and observations each day during the study to document the experience as well as ensure the participant was complying with the established protocols. The primary researcher encouraged the participant to ask questions at any point throughout the study.

Weeks Two and Four: Intervention Weeks

During weeks two and four, the participant completed two training intervention sessions each day (Monday through Friday), once in the late morning and again approximately three hours later in the afternoon. At the first Intervention Session on Monday of week 2, prior to beginning the general protocol, the participant received his Portable Neuromodulation Stimulator (PoNS™) device and education on the wear, care, and use of the device. The primary researcher answered the participant's questions and the participant explored the device to be comfortable and familiar with it prior to beginning the

protocol followed for the intervention weeks. After the participant expressed feeling comfortable with the device and had no further questions, the Intervention Sessions and following of the protocol began.

Each morning and afternoon Intervention Session included three 20-minute Targeted Training Activity Sessions. The three session included balance training, relaxation, and gait training. The participant used the PoNS™ device concurrently with balance and gait targeted trainings; the PoNS™ device was not used during the relaxation targeted training. All of the Targeted Training Activity Session tasks were personalized to the participant and depended on his ability levels each day as well as his limitations. As the participant mastered skills, the primary researcher increased the difficult level of tasks to maintain the just-right challenge. For example, once the participant was able to walk consistently in the center of the treadmill, the participant worked on reducing the number of times he dragged his left foot rather than clearing the treadmill surface. All targeted training activities were completed under the instruction and observation of the primary researcher.

Each day, prior to beginning the second Intervention Session, the participant completed the balance and gait assessments. These assessments were administered by the primary researcher and were videotaped and assessed by clinicians blinded to the study protocols. The participant journaled about his experiences. Each Friday, the participant also completed the GES-m, POPS, and CIQ. After completing the assessments, the rest of the afternoon Intervention

Session continued the same as the morning session with the three Targeted Training Activity Sessions for gait, relaxation, and balance.

Outside of the Intervention Sessions with the primary researcher, each day the participant completed two additional 20-minute CN-NINM training, one in the morning prior to work and one in the evening prior to bed. These sessions included less rigorous activities to ensure the participant's safety and increase likelihood of compliance. No targeted training activities or use of the PoNS™ device occurred on the weekends.

The decision to use one week interventions was based on previous laboratory observations of individuals with traumatic brain injuries. Often the individuals with TBIs responded quickly to the intervention.

If a trend is not able to be established during the five data points for the intervention, the intervention sessions for all following participants will be increased to two week interventions. This will result in a seven week commitment for participants instead of five weeks.

Weeks Three and Five: Withdrawal Weeks

During the third and fifth weeks, the participant did not use the PoNS™ device or complete any targeted training activities in order to document withdrawal effects of the CN-NINM intervention. Each afternoon (Monday through Friday), the participant completed the balance and gait assessments at approximately the same time as the second Intervention Sessions the week prior. On Friday afternoon, the participant completed the GES-m, POPS, and CIQ as

well. The researcher continued to encourage the use of daily journaling about changes noticed and experiences with the study.

Data Analysis

The principal guide and reference for completing data analyses came from guidelines established by Kratochwill et al. in 2010. The authors provide justification for each the methods of analysis, ensuring the results are evaluated in an appropriate and meaningful manner (Kratochwill et al., 2010).

Four primary means were used to evaluate the data collected: 1) visual analyses, also including; 2) basic trend lines using split middle celeration line; 3) percentage of data overlap technique; and 4) two standard deviation band analysis.

Visual Analyses

Data will be organized, graphed, and visually analyzed by the primary researcher to assess visual differences or discrepancies. To strengthen these results, an expert with a substantial single subject design analysis background will also visually analyze the data collected. This will be important to strengthen the observations made regarding the information since experts are recognized as better at interpreting single subject design data (Ottenbacher, 1986). Visual analyses can only reliably detect large effects in data (Parker & Hagan-Burke, 2007) and often have very poor inter-rater reliability and additional analyses methods are encouraged (Zhan & Ottenbacher, 2001). For these reasons, additional analyses will be completed as well.

To complete the visual analyses, there are six components to be evaluated within and between phases: 1) level; 2) trend; 3) variability; 4) immediacy of the effect; 5) overlap; and 6) consistency of data patterns across similar phases (Kratochwill et al., 2010).

Basic Trend Lines

Basic trend lines will be created for each phase of each participant and one technique used will be the split middle celeration line technique. Trend lines will be particularly beneficial in noting and explaining the trends during phases and noting changes in direction or slope (Solanas, Manolov, & Onghena, 2010).

Percentage of Data Overlap

A type of percentage of data overlap analyses will be used to evaluate adjacent phases (Parker, Vannest, & Davis, 2011). This form of analysis is able to state a percentage of one phase outside the prior phase. For example, if a line is drawn through the median of the baseline phase, and this line is below all the data points in the first intervention phase, it is easy and appropriate to state that 100% of data points from the first intervention phase were higher than the baseline phase.

Two standard deviation bands

The last type of analysis used will calculate the standard deviation in each phase; a line representing two standard deviations will be drawn below and above the data set. When continued into the adjacent phase, it is clear if any or how much of the data is more than two standard deviations different than the first phase. This analysis technique can be misleading if there is a great deal of

variability in the data, which further supports the use of several analysis techniques. Two standard deviations, in quantitative group designs, represents 95% of the population and indicated a 95% confidence that if something is outside of the two standard deviations it is truly different than the rest of the data, not that the difference is due to chance (Nourbakhsh & Ottenbacher, 1994).

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Appendix E: Pre-Screening

Screening Questionnaire

We are doing this study to learn more about the effects of a new therapeutic intervention tool (therapy aid). We want to study the immediate effects, what happens when the device is taken away, and what happens over a longer period of time. The intervention we are studying uses safe, mild electricity on your tongue to prepare your brain for learning while you do therapy activities. People who have used this device and completed other studies have had positive results. Almost all people have said they noticed their walking and balance getting better, and many have commented on other positive changes as well. A few people did not notice very much improvement in their walking or balance. No one has mentioned negative changes they believe are from the device.

If you want to be in this study, it will be a lot of work for you and a lot of time. You will have to come to a lab at the University of Wisconsin-Milwaukee (UWM) every day for 5 weeks to do a walking test and once a week you will do the same three additional surveys. If you miss too many days or on the rare chance the researcher thinks it is necessary, we might ask you to come an extra week, making the study a total of 6 weeks. Every other week, on the 1st, 3rd and 5th weeks, you will come to the lab every day to do a walking test. Each visit should take about 45 minutes. On the other two weeks, the 2nd and 4th, you will have to come to the lab twice every day, once in the morning and once in the afternoon. During these weeks, you will use the new intervention tool. Each appointment will be about an hour and a half so you will be in the lab a total of 3 hours each day during the two intervention weeks. You will also use the device at home two times per night, each time for 20 minutes. While you are using the

device, we will be helping you work on improving your balance and walking. You will do activities similar to what you did in rehabilitation in the hospital. For example you might stand on foam with your eyes closed to improve your balance, or walk backwards in the hallway to improve your walking. In both examples you would also keep the device on your tongue so it is providing the electricity to the tongue during the activities.

If you decide you want to be in the study, you can change your mind and drop out of the study at any time. There will not be any negative effects of you deciding not to be in the study anymore, but you will have to return the device.

Do you have any questions?

If you decide to be part of the study, there are two parts to the study. Phase I is the study I described to you before. It will last 5 weeks. If you finish that Phase and want to keep using the device, Phase II studies long-term effects. You will be able to keep the device and use it at home as much as you want, up to the amount you use it during the first Phase. Every six months for three years we will ask you to come back to the lab so we can see how your walking is and have you take three surveys. When you are using the device at home, we will ask you to put a mark on a calendar we give you every time you use the device. Again, you can stop participating in the study at any time. If you decide to stop, you will have to return the device. At the end of the three years, you will have to return the device.

Do you have any questions?

Are you interested in participating?

I am going to ask you several questions to make sure that you are an appropriate fit to the study. Please answer the questions as honestly as you can.

Questions

1. How old are you? _____
2. What caused your head injury? _____
3. How long has it been since your injury? _____
4. How much therapy have you had since your injury? _____
5. What kinds of rehabilitation have you had since your injury? _____
6. Approximately how long has it been since you received rehabilitation services?
7. Are you currently receiving any balance or walking (gait) training or in any exercise programs? _____
8. Are you your own legal guardian? _____
9. Do you live in any type of assisted living facility? _____
10. What type of support system do you have, who is your support system? _____

11. How would you describe your living situation? _____
12. Are you able to walk 30 feet[13] with or without an assistive device, such as a cane, walker or holding on to someone? _____
13. Are you able to maintain an upright posture for 20 minutes? _____
14. Do you have any electronic devices/implants such as a pacemaker, deep brain stimulator, biomechanical prosthetic? _____
15. Do you have any of the following conditions: a hard time understanding words you hear (called receptive aphasia), uncontrolled pain, uncontrolled mental health condition, another condition (or comorbid diagnosis) that affects balance such as Multiple Sclerosis or Parkinson's Disease, problems with your vision, myasthenia

- gravis, Charcot-Marie tooth disease, post-polio, guillan barre, fibromyalgia, hypertension, diabetes, or chronic fatigue syndrome? _____
16. Do you use tobacco products, have any contagious mouth diseases, sores, piercings or abrasions or tongue neuropathies? _____
17. Are you pregnant or trying to become pregnant? _____
18. Have you had a major change in the type or amount (dosage) of medications within the previous three months? _____
19. What kind of impairments to you still notice that you think are from your brain injury? (Some common symptoms noted are decreased balance and gait, ability to walk in a crowd, increased irritability, decreased short-term memory, decreased fine motor control, vision changes or impairments). _____

20. Are balance or walking activities hard for you? Some people have a hard time keeping their balance with their eyes closed, turning their head while walking, changing speeds or directions, or walking in a crowd. _____
21. Are you willing and able to come to the laboratory at the University of Wisconsin Milwaukee every day for five concurrent weeks? _____
22. Have you had any major life changes within the past month, or any events that affect your daily functioning? _____
23. In order to complete the longitudinal portion of the study, you must either have an email address or be willing to create an email address for the study. You do NOT need an email address to participate in the first phase. Do you have an email address? _____

Gait Improvement Intervention

Drug free intervention for individuals with previous traumatic brain injuries



- If you are no longer receiving therapy, do not use tobacco products, have a gait impairment, and are between 18-65, you may be eligible!
- The intervention uses a portable stimulator, rather than medications
- The intervention and testing will last 5 weeks. (Possible follow ups every six months for the following three years.)

If interested, contact Kati Liegl, UW-Milwaukee graduate student at kpliegl@uwm.edu or (414) 229-6803

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Appendix F: EqTDs

Equivalent text descriptions (EqTDs) are provided for each figure used in the research manuscript but are not included for the graphs created in Appendix C. Each of these graphs are described in context for trends and changes noted and will not be duplicated here.

Figure 1: Overview of CN-NINM terms

Brief Description: Flowchart defining terms intrinsic to the CN-NINM intervention

Essential Description: The flowchart shows two equations and has five components. The first equation is 20 minutes of Targeted Training Activity Session plus 20 minutes PoNS™ stimulation equals 1 CN-NINM session. The second equation is 3 CN-NINM sessions (gait, relaxation, balance) equals 1 Intervention session.

Figure 2: PoNS™ Device

Brief Description: Photograph of a PoNS™ device

Essential Description: The PoNS™ device has two main pieces. The first is a small plastic box with four buttons labeled “Down”, “Up”, “Off”, and “On”. A sticker labeling it PoNS™ is visible in the middle of the box. The second piece is a small oral tab. There is a plastic piece that is labeled to be just over one centimeter long and between one and two centimeters wide leading to an oral tab. The tab looks to have several small circles on it.

Figure 3: Participant using the PoNS™ device during gait CN-NINM session

Brief Description: Photograph of a woman walking backwards on a treadmill with the PoNS™ device in her mouth

Essential Description: The woman in the photograph is completing a gait training CN-NINM session with the PoNS™ device visible in her mouth. The device is small and the woman does not appear to be working to keep the device in her mouth, or focusing on the device or struggling to multitask. The device is attached to a lanyard which is around the woman's neck.

Figure 4: Romberg Stance

Brief Description: Photograph of a woman standing with her feet together

Essential Description: A woman is photographed standing with her feet next to each other, her arms folded into an "x" across her chest, and her eyes closed. This is the standardized position for completing the Romberg test.

Figure 5: Sharpened Romberg Stance

Brief Description: Photograph of a woman standing with one foot directly in front of the other

Essential Description: A woman is photographed standing with her feet in tandem (one in front of the other, with her heel touching her toes of the other foot), her arms folded into an "x" across her chest, and her eyes closed. This is the standardized position for completing the Sharpened Romberg test.

Figure 6: Participant completing the DGI task “Step over an Obstacle”

Brief Description: Photograph of a man stepping over a plaid covered shoebox

Essential Description: A man is stepping over a shoebox sized object covered in a plaid design. He is leading with his left foot. Another person is visible standing behind the man.

Figure 7: Participant completing CB&M Scale task “Step-Ups”

Brief Description: Photograph of a man stepping up onto a stair

Essential Description: A man is stepping up onto step. He appears to be leading with his left foot. Another person is visible to the side of the man.

Figure 8: Sharpened Romberg Best Time with Eyes Open

Brief Description: Graph of time scores on the Romberg test with eyes open showing five lines with alternating colors

Essential Description: Time scores for the Romberg test with eyes open are graphed with five points in each of five lines. The first line has three points on the highest point (60 seconds); the second line has four points at 60 seconds and the fifth point slightly below 60 seconds. The third line starts at about the 40 second line, drops slightly for the second point, then climbs steadily for the subsequent points, reaching 60 seconds on the final point. Each point on the fourth line is at 60 seconds. The second point on the fifth line is the only point not at 60 seconds, falling slightly above 50 seconds. Overall higher scores and greater stability is noted on the second and fourth weeks.

Figure 9: Best time on Sharpened Romberg with eyes closed

Brief Description: Graph of time scores on the Sharpened Romberg test with eyes closed showing five lines with alternating colors

Essential Description: Time scores for the Sharpened Romberg test with eyes closed are graphed with five points in each of five lines. The first line has four points between five and fifteen seconds and the fourth point is around 25 seconds. The first three points of the second line are between 15 and 25 seconds and the last two points around 5 seconds. The third line shows increase variability with a pattern similar to an “N” shape with scores ranging from 8-45 seconds, the second and fifth points near 45 seconds, and the first, third, and fourth points below 20 seconds. The fourth line is shaped like a “V” or “U” with scores ranging from 5-20 seconds. The fifth line has a pattern like an “M”, with high scores of 60 and just over fifty, respectively, and low scores between ten and twenty seconds. Overall trends show increasing variability over the five phases.

Figure 10: All scores from the Sharpened Romberg with eyes closed

Brief Description: Graph of each data point for the Sharpened Romberg test divided into Baseline, Intervention, Withdrawal, Intervention, and Withdrawal sections

Essential Description: Time scores for each day are graphed and sections are divided into baseline, intervention, withdrawal, intervention, and withdrawal. No obvious trends are noted in the data, however, the last phase has the most

variability and most of the data points for each phase are clustered at or under ten seconds.

Figure 11: Dynamic Gait Index Combined Scores

Brief Description: Graph of combined scores from the Dynamic Gait Index shown in five lines of alternating colors

Essential Description: Combined scores from the Dynamic Gait Index are graphed in five lines. Overall, a slight increasing trend is noted. The first line has high variability with scores ranging from 7-11 (with a maximum score of 12). The first point of the second line reaches 12 points, the maximum for the scale, and the last four points are 9 and 10 points. The third line scores have a “W” pattern with scores of 9 and 11. Scores on the fourth line are shaped like a “V” and range include scores of 12, 11, 10, 11, 12 respectively. The first point on the fifth line is 12 and all subsequent scores remain steady at 11.

Figure 12: Confidence Walking on Grass

Brief Description: Bar graph of Gait Efficacy Scale- modified scores with five lines of alternating colors

Essential Description: Five lines are graphed to show scores on the Gait Efficacy Scale-modified. Scores start at 4 points at the first line, increase one point for the second line, decrease one point at the third line, increase three points for at the fourth line, and increase one point at the fifth line.

Appendix G: IRB Forms

Jessica Rice
IRB Administrator
Institutional Review Board
Engelmann 270
P. O. Box 413
Milwaukee, WI 53201-0413
(414) 229-3182 phone
(414) 229-6729 fax

Modification/Amendment - IRB Expedited Approval

Date: April 29, 2013

<http://www.irb.uwm.edu>
ricej@uwm.edu

To: Roger O. Smith, PhD
Dept: College of Health Sciences

Cc: Kati Liegl

IRB#: 13.136

Title: Beneficial and Withdrawal Effects of Cranial Nerve Non-Invasive Neuromodulation on Functional Mobility for Individuals with Traumatic Brain Injury with Multiyear Follow-up

After review of your research protocol by the University of Wisconsin – Milwaukee Institutional Review Board, your protocol has received modification/amendment approval for:

- Addition of Independence First as a data collection site
- Addition of asking participants to consent to videotaping the gait assessment
- Revisions to consent forms to reflect the changes above

IRB approval will expire on **December 6, 2013**. If you plan to continue any research related activities (e.g., enrollment of subjects, study interventions, data analysis, etc.) past the date of IRB expiration, a Continuation for IRB Approval must be filed by the submission deadline. If the study is closed or completed before the IRB expiration date, please notify the IRB by completing and submitting the Continuing Review form found on the IRB website.

Unless specifically where the change is necessary to eliminate apparent immediate hazards to the subjects, any proposed changes to the protocol must be reviewed by the Institutional Review Board before implementation.

Please note that it is the principal investigator's responsibility to adhere to the policies and guidelines set forth by the University of Wisconsin – Milwaukee and its Institutional Review Board. It is the principal investigator's responsibility to maintain proper documentation of its records and promptly report to the Institutional Review Board any adverse events which require reporting.

Contact the IRB office if you have any further questions. Thank you for your cooperation and best wishes for a successful project

Respectfully,



Jessica Rice
IRB Administrator

IRBManager Protocol Form

Instructions: Each Section must be completed unless directed otherwise. Incomplete forms will delay the IRB review process and may be returned to you. Enter your information in the **colored boxes** or place an “X” in front of the appropriate response(s). If the question does not apply, write “N/A.”

SECTION A: Title

A1. Full Study Title:

Beneficial and Withdrawal Effects of Cranial Nerve Non-Invasive Neuromodulation on Functional Mobility for Individuals with Traumatic Brain Injury with Multiyear Follow-up.

SECTION B: Study Duration

B1. What is the expected start date? *Data collection, screening, recruitment, enrollment, or consenting activities may not begin until IRB approval has been granted. Format: 07/05/2011*

12/10/2012

B2. What is the expected end date? *Expected end date should take into account data analysis, queries, and paper write-up. Format: 07/05/2014*

09/30/2017

SECTION C: Summary

C1. Write a brief descriptive summary of this study in Layman Terms (non-technical language):

Functional recovery from neurological insult or disease remains compromised for many individuals. In the field of neurorehabilitation, electrical stimulation of the brain has long been theorized as a potential mechanism to improve function. Recently, researchers at the Tactile Communication and Neurorehabilitation Laboratory at the University of Wisconsin- Madison (TCNL) have developed a method of delivering non-invasive electrical stimulation to the brain that, when paired with targeted rehabilitation training (cranial nerve non-invasive neuromodulation, or CN-NINM), is showing remarkable benefits and promise for rehabilitation. As a portable device to deliver the stimulation continues to be developed, observational, case study and proof of concept investigations plus one randomized controlled trial (RCT) are reported. This study will use a single subject research design, appropriate at this stage of concept development, to quantify the effect of CN-NINM in improving functional balance and gait in individuals who have residual effects following a traumatic brain injury (TBI).

Background: Multiple studies have examined the effects of the CN-NINM intervention for multiple diagnostic groups, but this is the first study that proposes to examine the withdrawal effects from the intervention as well as the immediate effects. The CN-NINM

intervention, created by TCNL at the University of Wisconsin-Madison, combines non-invasive, safe doses of electricity, applied to the tongue using a device called the Portable Neurostimulator (PoNS™), and personalized targeted training activities. All of the completed research has looked specifically at individuals with balance and/or gait impairments and have focused targeted training activities to reduce these impairments. fMRI research has demonstrated an increase in activation in the posterior aspect of the pons varolli, superior medulla oblongata, and ventral cerebellum after a week of CN-NINM intervention; these areas are primary sensory integration and movement control centers, thus making them prime targets for neuromodulation to improve balance and gait impairments. Prior research has studied effects of this intervention for individuals with primary vestibular dysfunction, cerebellar atrophy, traumatic brain injuries, strokes, and Multiple Sclerosis. This research has demonstrated significant positive results for each population tested, and have yet to observe negative side effects from the intervention. Some of the results appeared to have a carryover effect, lasting after the stimulation was stopped. The withdrawal effects have not been studied. This study will look at the benefits and withdrawal effects of the CN-NINM intervention for individuals with a past traumatic brain injury as well as follow-up on functional balance and gait changes every 6 months for three years.

Research utilizing electrical stimulation of the tongue has established the technique as safe and easy to administer. No negative side effects have been recorded. Through research using sensory substitution and the BrainPort™, the predicate device to the PoNS™, researchers observed improvements in participants' function that did not appear related to the intervention received. Examples of these improvements included improved balance and gait, improved mood, concentration, sleep, and a reduction in expressive aphasia and reduction in pain. The CN-NINM intervention was established to explore the effects of using information-free stimulus combined with targeted training specific to the individuals' impairments.

Design: The proposed study will use a single subject design with four participants to study the benefits and withdrawal effects of the CN-NINM intervention using an A-B-A-B-A design planned to last 5 weeks. CN-NINM involves targeted therapeutic interventions paired with simultaneous non-invasive electrical stimulation. Within any phase, should two data points be greater or less than the value of two minimal detectable changes (16 point change for the gait assessment) from the regression line, that phase will be lengthened to two weeks. This is not anticipated unless the participant is unable to attend his/her appointments more than once in a week. Therefore, phase lengths will be referred to as lasting one week, however it is possible that a phase may last a maximum of two weeks in a rare event.

Following this, should the participant decide to continue with the second phase of the study, a longitudinal follow up every 6 months for three years will provide descriptive information regarding functional status and voluntary use of the device outside of a structured study environment. (See the timeline protocol for participant expectations and the overall study design.)

All researchers with participant contact have a formal education in therapeutic rehabilitation, as well as experience working with people with disabilities including brain injuries. The primary researcher has 6 months of full time clinical experience with populations in physical rehabilitation including working with individuals with brain injuries. In addition to the clinical experience, the primary researcher has completed substantial formal education in rehabilitation areas. The primary researcher will be trained on the intervention and participant interactions by a CN-NINM expert. The primary researcher will receive training at TCNL from a primary researcher of a study using the CN-NINM intervention at TCNL. Training will continue until the primary researcher and expert reach agreement in answering potential questions and completing appropriate targeted training activities. This training will occur prior to any data collection with participants in the study. During the study, several experts from TCNL and the R₂D₂ Center will be available for questions, should any arise.

Baseline: The initial baseline phase will contain 6 days of data collection. On the first data collection day, participants will read and sign the Informed Consent, complete the Participant Objective Participation Subjective (POPS) Assessment, Community Integration

Questionnaire (CIQ), modified Gait Efficacy Scale (GES-m), and Community Balance and Mobility (CB&M) Scale. Of the measures used, all are self-report assessments which will be taken by the participant independently in the lab, except the CB&M Scale, which will be administered by a trained researcher. The first day will take approximately 90 minutes. The subsequent five days of data collection for the baseline will occur on a following Monday through Friday in the afternoons. Monday through Thursday, participants will be assessed only with the CB&M Scale. On Friday, participants will complete the gait assessment as well as the three self-assessment surveys. The CB&M Scale will be videotaped contingent on participant consent to videotape. If the participant does not consent to being videotaped, they may still participate in the study with no negative consequences. During the baseline phase, participants will be instructed to continue with their normal daily routines and structures, trying not to change their habits in an attempt to do better on the assessments. Each day, data collection will take approximately 45 minutes, except appointments that include the self-assessment surveys, which will take approximately 90 minutes. All appointments will occur at a University of Wisconsin – Milwaukee laboratory in the R₂D₂ Center or in the Occupational Sciences & Technology (OS&T) Department or in an equivalent space at Independence First. These spaces are well-equipped and have been used previously for human subjects research. They provide ample space to complete the balance, gait and relaxation training. The gait assessment will be completed either inside the primary data collection areas or in the hallway directly outside.

Intervention: The “B” phases indicate the intervention phases. Each intervention phase lasts 5 days. On the first day of the intervention phase, participants will receive a PoNS™ device and be instructed on proper wear, care, and use of the device. Each day of the Intervention phases, participants will complete two intervention sessions in the laboratory under the direction of a trained researcher, one in the morning, the other in the afternoon approximately two to three hours apart. Each intervention session will include three 20 minute targeted training activities, one for balance, one for relaxation, and the third for gait (completed in the order listed. See attachment of typical training activities for examples of typical training activities.). Participants will use the PoNS™ device to provide electrical stimulation during the balance and gait targeted training activities. These targeted training activities are selected to replicate the intervention used in earlier studies at the TCNL. Each targeted training activity session will be individualized based on the functioning of the participant. Activities will be selected to be challenging but feasible for participants, and will change in difficulty level as the participant’s ability level changes. The risk associated with completing the activities is no more than the risk in clinic based outpatient neurorehabilitation. The CB&M Scale will be administered prior to beginning the second intervention session. This assessment will be videotaped contingent on participant consent to videotape. If the participant does not consent to being videotaped, they may still participate in the study with no negative consequences. Each intervention session will take approximately 90 minutes to complete. On the last day of the intervention phases, participants will also complete the self-assessment surveys after the completion of the CB&M Scale. Participants will be encouraged to document their experiences with the intervention throughout the study, but the journaling will not be structured or regulated. The journaling will be collected and reviewed weekly to ensure compliance and identify any potential problems or confounding variables such as illnesses or major life changes. Each day, participants will be asked about any adverse effects from the intervention.

In addition to the two intervention sessions in the laboratory, participants will use the PoNS™ device for two 20 minute sessions at home in the evenings while completing more simplified tasks to ensure safety completing the tasks. The participants will select which training activities they complete in the evenings.

Withdrawal: The “A” phases indicate withdrawal phases. Both withdrawal phases last five days. During the withdrawal phases, participants will come to the laboratory in the afternoon. Each day, participants will be assessed using the CB&M Scale. This assessment will be videotaped contingent on participant consent to videotape. If the participant does not consent to being videotaped, they may still participate in the study with no negative consequences. On the last day of the withdrawal phases, participants will also complete the GES-m, CIQ, and POPS after the CB&M Scale. Each appointment is expected to last

approximately 45 minutes, with the visit on the last day lasting approximately 90 minutes. Participants will be encouraged to maintain as similar a routine and habits as they had prior to admittance into the study.

After the last withdrawal period, participants will be allowed to choose if they would like to keep the device and participate in the longitudinal portion of the study. If the participants decide not to continue with the research, they will be asked to return the device and no additional information will be collected on that participant. If the participant chooses to keep the device and continue with the study, they will complete the follow-up sessions described below. The longitudinal information collected will be used as descriptive information.

Overall, the first, third, and fifth weeks will require 45 minute daily sessions Monday through Thursday, and 90 minute sessions on Fridays. In addition, the first appointment will occur prior to starting the first full week; this appointment may take up to 90 minutes. The second and fourth weeks require two laboratory sessions daily, each approximately 90 minutes, totaling approximately three hours per day in the laboratory both weeks.

Longitudinal Follow-ups: After the completion of the ABABA protocol, subjects will be asked if they wish to continue use of the PoNS™ device. If they want to continue using the device there will be no further formal intervention and minimal recording will informally document use. Participants will be provided with monthly calendars. Each time they use the device, participants will indicate this on the calendar by marking the day with an “x”. Participants will be informed that they can use the device daily up to the amount they used during the initial phase of the study or rarely use the device; the amount of use is of no consequence so long as they accurately record how often they choose to use the device. Participants will receive monthly email reminders to continue tracking the use of the PoNS™ device. Monthly email reminders will also encourage and welcome periodic updates on functional status and experience with the device. (See the sample monthly email in the supplemental information.) If participants choose to stop using the device, they will be asked to return the device. Every six months for the following three years, participants will return to the laboratory to complete the CB&M Scale, GES-m, CIQ, and POPS. Participants will also be instructed to bring their calendars to the researchers in order to track voluntary usage and functional status changes. Subjective journaling as in the ABABA protocol will be encouraged but not required; the back side of the calendar page will have room for subjective journaling or comments. Each follow up visit will be expected to last for approximately 90 minutes.

Phase I will last until four subjects have completed the phase. This is expected to require up to approximately six months of data collection. Phase II will be conducted for up to three years from the time the last (fourth) participant successfully completes Phase I.

Data Collection: All data collection will occur at a laboratory at UW-Milwaukee in the R₂D₂ Center or in the OS&T Department or at IndependenceFirst. The UWM spaces have previously been used for human subjects data collection and both areas include spaces that provide a quiet location for the balance and relaxation training. They also have space to complete the balance and gait trainings. (1) The primary outcome measure is the Community Balance & Mobility Scale (CB&M Scale), a gait assessment created for individuals with TBI who are ambulatory in the community and have gait impairments not detectable with other measures. (2) A modified version of the Gait Efficacy Scale will be used after each phase and during follow-up visits to examine the effects of the intervention on the confidence participants have completing routine functional gait tasks. (3 & 4) The POPS and CIQ will be administered at the first visit, at the end of each phase, and at each follow-up visit. These measures will be used to examine community integration. (5) Participants will also keep informal journals during the study to document their experiences with the intervention. During intervention weeks, the assessments will be completed prior to beginning the afternoon intervention session. During withdrawal weeks, participants will come to the laboratory in the afternoon to complete the assessments.

If a participant completes the study at Independence^{First}, the researcher will be in possession of the paper copies of data collected at all times. After the completion of trainings or the assessments each day, the records collected will be taken directly to the secured location at UWM. No additional personnel will have access to the information collected from Independence^{First} or UWM.

The participant data (video-recorded) will be assessed by two trained raters, each with clinical experience. The two raters will complete a training session together to become familiar with the assessments. The raters will score the assessments either at UWM in the R₂D₂ Center or in their office with instructions for maintaining the confidentiality of the participant. If the rater chooses to complete the scoring outside of UWM, a CD/DVD of the videos will be personally delivered to the rater. They will be expected to return the CD/DVD upon completion of the scoring, up to one month after obtaining the CD/DVD and immediately after completing the scoring. None of the scored information obtained from the raters will contain patient identifying data. The raters will be compensated for their time scoring the data.

Participants: Four participants with a history of a closed traumatic brain injury will complete Phase I of the study. If a participant drops out during Phase I of the study, that participant will be replaced until four participants successfully complete Phase I (up to a maximum of 12 participants recruited). A maximum of the four participants that complete Phase I will be eligible to complete Phase II; participants who drop out during Phase II will not be replaced and beginning Phase II is not required. Participants must live in a community setting and no longer be receiving rehabilitation services or balance training. For inclusion and exclusion criteria, see D3. Participants will be recruited through flyers hung in the community, referrals, word of mouth, and email flyers sent to targeted brain injury support groups, (see recruitment flyers in attachments).

C2. Describe the purpose/objective and the significance of the research:

This research will evaluate the benefits and withdrawal effects of the CN-NINM intervention on functional gait for individuals with TBI. The intervention protocol used in this study is based on the protocols and research of the PoNS™ device developers at TCNL. Their work has demonstrated significant benefits, particularly improved balance and gait, through preliminary case study and proof of concept studies, for individuals with diverse neurological diagnoses. One randomized controlled trial is completed with subjects who have Multiple Sclerosis. To date, there have been no formal investigations looking at the effects of withdrawal. CN-NINM has the potential to greatly impact rehabilitation, but it is critical to understand and document withdrawal effects. This is an important component to understand prior to FDA trials. The longitudinal component to the study will provide structured, quantitative and descriptive information on the longitudinal effects as well as track voluntary participant usage.

C3. Cite any relevant literature pertaining to the proposed research:

Bach-y-Rita, P., & Kercel, S. W. (2003). Sensory substitution and the human-machine interface. *Trends in Cognitive Sciences*, 7(12), 541-546. doi: 10.1016/j.tics.2003.10.013

Badke, M. B., Sherman, J., Boyne, P., Page, S., & Dunning, K. (2011). Tongue-based biofeedback for balance in stroke: Results of an 8-week pilot study. *Archives of Physical Medicine & Rehabilitation*, 92, 1364-1370.

Cramer, S. C., Sur, M., Dobkin, B. H., O'Brien, C., Sanger, T. D., Trojanowski, J. Q., . . . Vinogradov, S. (2011). Harnessing neuroplasticity for clinical applications. *Brain*, 134, 1591-1609. doi: 10.1093/brain/awr039

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Dimyan, M. A., & Cohen, L. G. (2011). Neuroplasticity in the context of motor rehabilitation after stroke. *Nature Reviews Neurology*,

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SECTION D: Subject Population

Section Notes...

- D1. If this study involves analysis of de-identified data only (i.e., no human subject interaction), IRB submission/review may not be necessary. Visit the Pre-Submission section in the [IRB website](#) for more information.

D1. Identify any population(s) that you will be specifically targeting for the study. Check all that apply: (Place an "X" in the column next to the name of the special population.)

Not Applicable (e.g., de-identified datasets)	Institutionalized/ Nursing home residents recruited in the nursing home
UWM Students of PI or study staff	Diagnosable Psychological Disorder/Psychiatrically impaired
Non-UWM students to be recruited in their educational setting, i.e. in class or at school	Decisionally/Cognitively Impaired

	UWM Staff or Faculty	Economically/Educationally Disadvantaged
	Pregnant Women/Neonates	Prisoners
	Minors under 18 and ARE NOT wards of the State	Non-English Speaking
	Minors under 18 and ARE wards of the State	Terminally ill
X	Other (Please identify): Individuals with a gait impairment secondary to a closed traumatic brain injury but not currently receiving any type of balance intervention or therapy.	

D2. Describe the subject group and enter the total number to be enrolled for each group. For example: teachers-50, students-200, parents-25, parent’s children-25, student control-30, student experimental-30, medical charts-500, dataset of 1500, etc. Enter the total number of subjects below.

Describe subject group:	Number:
Individuals with previous traumatic brain injury	12
TOTAL # OF SUBJECTS:	12
TOTAL # OF SUBJECTS (If UWM is a collaborating site):	

D3. List any major inclusion and exclusion criteria (e.g., age, gender, health status/condition, ethnicity, location, English speaking, etc.) and state the justification for the inclusion and exclusion:

<p>Inclusion Criteria</p> <ul style="list-style-type: none"> • Have a clinically detectable gait impairment secondary to a closed traumatic brain injury • Live in a community setting or facility that does not provide assistance • No longer be receiving rehabilitation or balance training programs of any kind • Be able to ambulate 10 meters without resting • Be able to maintain upright posture for 20 minutes • Be between the ages of 18-65 • Speak fluent English • Must be their own legal guardian and able to understand instructions and give informed consent <p>Exclusion Criteria Participants will be excluded from the study if they:</p>
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- have electrical devices/implants such as pacemakers
- have a biomechanical prosthetic
- have a comorbid diagnosis that could affect balance such as Multiple Sclerosis or Parkinson’s Disease
- are pregnant or trying to become pregnant
- use tobacco products
- have contagious mouth diseases, sores, piercings or abrasions
- have tongue neuropathies
- have receptive aphasia
- have uncontrolled pain
- have uncontrolled mental health conditions
- have a history of seizures, including a diagnosis of Epilepsy
- self-report as having a vision impairment that is not corrected
- are on medications and have had a major change in type or dosage within three months of enrollment
- lack the motivation necessary to complete the tasks
- lack the cognition to understand and complete the protocols as directed
- do not have an email address and are unwilling to create one (this applies only if participants choose to complete Phase II of the study. An email address is not required for the first phase.)

SECTION E: Informed Consent

- Section Notes...**
- E1. Make sure to attach any recruitment materials for IRB approval.
 - E3. The privacy of the participants must be maintained throughout the consent process.

E1. Describe how the subjects will be recruited. (E.g., through flyers, beginning announcement for X class, referrals, random telephone sampling, etc.). If this study involves secondary analysis of data/charts/specimens only, provide information on the source of the data, whether the data is publicly available and whether the data contains direct or indirect identifiers.

Participants will be recruited through flyers distributed in public community locations as well as word of mouth and referrals. Emails with flyers attached will be sent to targeted groups. These groups will include TBI support groups such as Dryhooch (a coffee shop for veterans, ran by veterans that utilizes various peer-support support groups) and Brain Injury Alliance of Wisconsin. Recruitment will continue until four participants complete the five week section of the study; if a participant drops out of the study, an additional participant will be recruited to complete the study.

E2. Describe the forms that will be used for each subject group (e.g., short version, combined parent/child consent form, child assent form, verbal script, information sheet): If data from failed eligibility screenings will be used as part of your “research data”, then these individuals are considered research subjects and consent will need to be obtained. Copies of all forms should be attached for approval. If requesting to waive documentation (not collecting subject’s signature) or to waive consent all together, state so and complete the “Waiver to Obtain-Document-Alter Consent” and attach:

Participants will complete an Informed Consent Form prior to participation. Prior to signing the consent form, information will be explained to the participant orally by the primary researcher, a copy will be provided for the participant to keep, and the participant will have time to read the document prior to signing, returning the document to the primary researcher and beginning the study.

E3. Describe who will obtain consent and where and when consent will be obtained. When appropriate (for higher risk and complex study activities), a process should be mentioned to assure that participants understand the information. For example, in addition to the signed consent form, describing the study procedures verbally or visually:

Participants interested in completing the study will contact the researchers. A phone screening will determine eligibility and provide the opportunity for questions and answers. If eligible, the participant will schedule a time to begin the study at a University of Wisconsin-Milwaukee laboratory or at IndependenceFirst. The primary researcher will again explain each section of the study and Informed Consent for Phase I. After the explanation, the participant will be provided time to read and ask questions regarding the Phase I consent form prior to signing the form, returning it to the primary researcher, and beginning the study. Each participant will be provided a copy of the Informed Consent to keep. If the participant decides to continue to participant in Phase II of the study, the Informed Consent for Phase II will be explained and provided to participants in the same manner as the Informed Consent for Phase I. Both of the two phases in the study have a separate Informed Consent document.

SECTION F: Data Collection and Design

Section Notes...

- F1. Reminder, all data collection instruments should be attached for IRB review.
- F1. The IRB welcomes the use of flowcharts and tables in the consent form for complex/ multiple study activities.

F1. In the table below, chronologically describe all study activities where human subjects are involved.

- In **column A**, give the activity a short name. E.g., Obtaining Dataset, Records Review, Recruiting, Consenting, Screening, Interview, Online Survey, Lab Visit 1, 4 Week Follow-Up, Debriefing, etc.
- In **column B**, describe in greater detail the activities (surveys, audiotaped interviews, tasks, etc.) research participants will be engaged in. Address where, how long, and when each activity takes place.
- In **column C**, describe any possible risks (e.g., physical, psychological, social, economic, legal, etc.) the subject may **reasonably** encounter. Describe the **safeguards** that will be put into place to minimize possible risks (e.g., interviews are in a private location, data is anonymous, assigning pseudonyms, where data is stored, coded data, etc.) and what happens if the participant gets hurt or upset (e.g., referred to Norris Health Center, PI will stop the interview and assess, given referral, etc.).

A. Activity Name:	B. Activity Description:	C. Activity Risks and Safeguards:
Screening	Interested participants will contact the researcher and a preliminary phone screening will determine eligibility and detail	Risks: Loss of confidentiality Safeguards: Screenings will be completed by the

	requirements for the study.	primary researcher and information will be stored on a password protected computer. Only the primary researcher and project advisor will have access to the information. Phone screen information of individuals who do not qualify or do not wish to participate will be destroyed.
First visit	At the UWM lab or Independence <i>First</i> research space, informed consent will be obtained. After signing, the CB&M Scale, CIQ, POPS and GES-m will be given to document the current level of gait function and other self-reported functional statuses. The first visit will take approximately 90 minutes.	Risks: Loss of confidentiality of information, risk of falling Safeguards: Any identifying information for participants will be accessed by only the primary researcher and administrators. If conducted at Independence <i>First</i> , information will be taken to UWM each day after the completion of the participant interaction. Information will be stored on a password protected computer. Subjects will be given a research participant number for the study and only the number will be used on data collection forms. All participant information files will be encrypted upon storage on the server. All assessments will be administered by a trained researcher. Assessment tasks will only be completed if they are felt to be safe for the participant. Participants will be asked to wear a gait belt at the researcher's discretion to increase safety. Researchers will maintain proximity to the participants when completing the gait assessment and balance and gait trainings, as appropriate.
Baseline visits (visits during the first week)	Participants will complete the gait assessment under the observation and direction of a trained researcher to ensure safety. This will be videotaped if the participant consents.	Risks: Falls during the CB&M Scale, loss of confidentiality Safeguards: The CB&M Scale will be completed

	<p>Participants will also complete the GES-m, POPS, and CIQ on the last day of the phase to assess confidence completing various common routine tasks. Each baseline visit will take approximately 45 minutes.</p>	<p>under the supervision of a trained researcher to ensure safety. Participants will be asked to wear a gait belt at the researcher's discretion to increase safety. Researchers will maintain proximity to the participants when completing the gait assessment and balance and gait trainings, as appropriate. Identifying information will not be kept with data, and all information will be stored on a password protected computer and only the primary researchers and administrators will have access to identifying information. All participant information files will be encrypted upon storage on the server.</p>
<p>Intervention visits (visits during the 2nd and 4th weeks)</p>	<p>Portable neurostimulator (PoNS™) devices will be provided to each participant and they will be instructed on proper wear, care, and usage. Participants will complete the CB&M Scale daily (which will be videotaped with participant consent) and the GES-m, POPS, and CIQ at the end of each intervention phase. Participants will complete two intervention sessions per day with the assessment(s) completed at the beginning of each afternoon session. Each intervention session will take approximately 90 minutes and will be under the direction of a trained researcher.</p>	<p>Risks: Falls, discomfort, negative reaction to the PoNS™ device, decrease in function, loss of confidentiality Safeguards: Training activities will be personalized to each participant to provide an appropriate challenge without increasing the risk of falls. Training will be done under the direction of a researcher. Participants will be asked to wear a gait belt at the researcher's discretion to increase safety. Researchers will maintain proximity to the participants when completing the gait assessment and balance and gait trainings, as appropriate. Participants will be educated on the appropriate use and handling of the device to reduce the likelihood of discomfort while using it. Should any discomfort occur, participants will be asked to explain to ensure it is caused from the device. Any discomfort or negative effect from the device will be recorded and</p>

		<p>carefully observed. Any negative reactions will be discussed with the project advisor, primary researcher, participant, and intervention experts. There have been no indications in any previous or related research that participants will experience negative effects. Similarly, there is no indication from prior research that participants will observe a decrease in function. All participant information files will be encrypted upon storage on the server. Participants will be free to withdraw from the study at any time should they so decide.</p>
<p>Withdrawal visits (visits during the 3rd and 5th weeks)</p>	<p>Participants will be assessed on the CB&M Scale under the direction of the trained researcher to ensure safety (this will be videotaped with participant consent). On the last days of the weekly phases, participants will complete the GES-m, CIQ, and POPS. Participants will not have the PoNS™ device during these weeks and will be instructed not to modify their habits, performing as they typically did prior to entering the study; they will be instructed not to continue completing the targeted training activities. Each visit will take approximately 45 minutes.</p>	<p>Risks: Falls, loss of confidentiality, decrease in gait function Safeguards: All gait measures will be completed under the direction of a trained researcher to ensure safety. Participants will be asked to wear a gait belt at the researcher's discretion to increase safety. Researchers will maintain proximity to the participants when completing the gait assessment and balance and gait trainings, as appropriate. Identifying information will not be kept with data, and all information will be stored on a password protected computer. All participant information files will be encrypted upon storage on the server. No research has documented withdrawal effects. However, if gait function should decrease, participants will be allowed to resume use of the device after the study should they choose to do so.</p>

<p>Longitudinal Follow-up: Monthly reminders</p>	<p>Participants will receive monthly emails to remind them to fill out their daily tracking log (indicating whether they used the device that day or not and how many times). The reminders will also encourage periodic informal updates on their experiences and functioning or feedback regarding the device and any questions they may have.</p>	<p>Risks: Loss of confidentiality, discomfort using the device. Safeguards: Identifying information will not be stored with participant data. All information collected will be stored on a password protected computer. Should any negative side effects or discomfort occur, participants are free to ask questions to the researchers as well as stop using the device with no negative consequences. Negative effects from the intervention will be documented and discussed with the participant, primary researcher, project advisor and intervention experts.</p>
<p>6 month follow-ups</p>	<p>Participants will return to the laboratory to complete the same assessments they completed on the first day of the study (the CB&M Scale, GES-m, POPS, and CIQ). This session should take approximately 90 minutes to complete. Participants will be asked to bring any subjective journaling they completed during the 6 month period as well as the monthly calendars tracking their usage of the PoNS™ device.</p>	<p>Risks: Loss of confidentiality, risk of falls, Safeguards: All information will be collected by a trained researcher and identifying information will not be stored with participant data. All information collected will be stored on a password protected computer. All assessments will be completed under the direction of a trained researcher. Participants will be asked to wear a gait belt at the researcher's discretion to increase safety. Researchers maintain proximity to the participants when completing the gait assessment and balance and gait trainings, as appropriate.</p>
<p>Last 6 month follow-up visit at three years</p>	<p>Participants will be asked to return the device. If, after three years, in the unlikely event that the device is not FDA approved and a participant remains dependent on using the device, researchers will consider extending the study to continue tracking the individual.</p>	<p>Risks: Loss of confidentiality, discomfort returning the device. Safeguards: Identifying information will not be stored with participant data. As noted in description, if a participant remains dependent on the device after 3</p>

		years, researchers will consider extending the study to continue tracking use.
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F2. Explain how the privacy and confidentiality of the participants' data will be maintained after study closure:

All data will be initially collected on paper forms, which will be stored in a locked cabinet in a locked room the researcher's lab. If participants complete the study at Independence^{First}, the forms and video from the assessment will be taken directly to UWM daily after the completion of the trainings or assessments for each day. The forms will remain in the possession of the researcher until they are secured in the locked cabinet at UWM. Information will be coded into spreadsheet forms and stored confidentially on a password protected server. In addition, all documents that are stored on the server as well as backup data will be encrypted using a virtual encryption disk as the documents are being saved to the secure server. All information will be destroyed five years after the completion of data collection for the study. All information will be stored confidentially and no identifying information will be associated with information gathered from the study. All participants will be assigned a number, and information will use the participant's number rather than identifying information. Only the lead researchers and administrators will have access to identifying information.

F3. Explain how the data will be analyzed or studied (i.e. quantitatively or qualitatively) and how the data will be reported (i.e. aggregated, anonymously, pseudonyms for participants, etc.):

Data analyses will follow the Kratochwill standards and analysis methods may include visual analyses, trend lines, split middle celebration lines, and the percentage of overlap techniques. Qualitative information will also use thematic identification methods. All information will remain confidential and identifying information will not be published or distributed. Any publication or presentation of the information will be deidentified.

Two trained raters, each with clinical experience and human subjects training, will evaluate the data. Raters will review the video data at their office or at UWM. Raters will be provided with a CD/DVD of the data if they choose to rate the data outside of UWM. The video will contain the participants face, but the raters will not receive any information about the participant and none of the data they score involves sensitive information. The CD/DVD will be returned upon completion of the scoring, no more than one month after obtaining the CD/DVD. The scored data obtained from the rater will not have any sensitive information, including any demographic information. The raters will be instructed on methods for maintaining confidentiality of the participant during the viewing and possession of the video data. Raters will be instructed to score data when they are alone in an area and store the information in a locked, protected location. All raters will have human subjects training and the DVD will be personally returned to the student researcher.

SECTION G: Benefits and Risk/Benefit Analysis
<p>Section Notes...</p> <ul style="list-style-type: none"> Do not include Incentives/ Compensations in this section.

G1. Describe any benefits to the individual participants. If there are no anticipated benefits to the subject directly, state so. Describe potential benefits to society (i.e., further knowledge to the area of study) or a specific group of individuals (i.e., teachers, foster children). Describe the ratio of risks to benefits.

Potential benefits for participants include an improvement in functional gait during the intervention weeks which may lead to carryover past the intervention weeks. Participants will be allowed to choose the amount they use the device during the longitudinal section of the study, and may experience improved function with increased carryover time. In previous research, many participants noted improvements in other areas in addition to improvements in balance and gait. This is possible for individuals in the current study and previous improvements appear to be dependent on the other limitations the individual has. By participating in the study, participants are contributing to further knowledge regarding the withdrawal and longitudinal effects of the CN-NINM intervention, and potentially leading to significant discoveries and more effective interventions for individuals with gait impairments. The potential benefits of the study outweigh the risks.

G2. Risks to research participants should be justified by the anticipated benefits to the participants or society. Provide your assessment of how the anticipated risks to participants and steps taken to minimize these risks, balance against anticipated benefits to the individual or to society.

Potential risks to participants are minimal. Previous research has demonstrated the safety of the PoNS™ neuromodulation device and has used the protocol proposed. The FDA has determined that the predecessor for the current device, the BrainPort™, is a nonsignificant risk device. The risk of discomfort or harm from the use of electricity is very slim. There have been 14 IRB protocols approved at the University of Wisconsin-Madison using the PoNS™ device or predicate device, the BrainPort™. The device development has been ongoing for the previous 14 years. (See supplemental information for a listing of all the approved IRB protocols, additional information regarding technical details of the PoNS™, and the nonsignificant risk letter from the FDA for the BrainPort™) The device is battery powered, thereby ensuring the discharge of a regulated amount of electricity at a time. When recharging the device, the device is not capable of discharging stimulation. Each time the device is turned off, the intensity resets; when the device is turned on it is always at the lowest intensity setting (below perception level) and participants control setting the intensity each time they begin to use the device. Participants are in control of the device and the intensity of the stimulation at all times during the study. If the stimulation for any reason becomes uncomfortable, participants will be encouraged to reduce the intensity, turn the device off, and/or remove the device from their mouth at any point.

Participants will use the PoNS™ device independently and without supervision during intervention weeks as well during the longitudinal component of the study. Participants will receive thorough training as to the proper use, care, and handling of the device. There have been no previous reports of any negative effects due to overuse or misuse of the device. Participants will be instructed to not let anyone else use their device, as the devices are not intended to share between people and the other individual may not meet inclusion and exclusion criteria. Aside from misuse due to sharing the device, there is no other known risk to using the device without supervision after the initial training.

Participants may face a slight risk of falling during interventions and assessments. This risk is no more than in a clinical neurorehabilitation setting. This study will be conducted under the direction of a licensed occupational therapist, and participants will be under the direct direction of a trained researcher to ensure they are following safety instructions during treatments. All researchers with participant contact have a formal education in a therapeutic rehabilitation and background, as well as experience, working with people with disabilities. A researcher will be near the participants during trainings and the gait assessment to provide safety instructions and hands-on stabilization if necessary. Researchers will use clinical judgment to avoid unsafe activities that may increase the risk of falls. Participants will wear a safety/gait belt as necessary during gait or balance tasks if the researcher feels he/she needs additional hands on support during tasks. Not all participants are expected to require the use of a gait belt, as the participants will all be able to ambulate independently and training tasks will be customized to meet their ability level.

In the unlikely event that a participant falls during the time in the laboratory, the test or training will stop immediately and the

situation will be assessed. If the participant is injured in any way, emergency care will be called. The participants will be responsible for any costs accrued as a result of the emergency care. This study and UW-Milwaukee make no commitment to provide compensation for a research-related injury. Participants may contact the study advisor with questions or further concerns.

In addition, if at any time there are indications that the patient is in distress, the training session will be stopped immediately, and both the circumstances and the plans for progression will be evaluated and discussed with the participant, study advisor, and experts from TCNL, as appropriate. Participants are free to withdraw from the study at any time without penalty or explanation. Participation in this study will not interfere with insurance coverage for the participant. No harmful effects have been observed in any participants who have used the PoNS™ or BrainPort™ devices for individuals receiving additional medical treatments. Several medical conditions that may require medical treatment (such as MS and Parkinson's Disease) are exclusion criteria. However, there is no indication that the therapeutic intervention using the PoNS™ device with targeted training will negatively impact individuals who are receiving additional medical treatment.

Any adverse event will be reported to the IRB in writing within five working days. Any serious adverse event (an event that is life-threatening regardless if associated with the study) will be reported immediately to the IRB. All adverse events, serious and non-serious, will be fully documented on the appropriate report forms. The primary researcher or study advisor will report all potential adverse events, For each adverse event, the PI will provide the onset, duration, intensity, treatment required, outcome, and action taken.

Any new complications not already reported that may impact willingness to participate will be reported to participants.

SECTION H: Subject Incentives/ Compensations

Section Notes...

- H2 & H3. The IRB recognizes the potential for undue influence and coercion when extra credit is offered. The UWM IRB, as also recommended by OHRP and APA Code of Ethics, agrees when extra credit is offered or required, prospective subjects should be given the choice of an equitable alternative. In instances where the researcher does not know whether extra credit will be accepted and its worth, such information should be conveyed to the subject in the recruitment materials and the consent form. For example, "The awarding of extra credit and its amount is dependent upon your instructor. Please contact your instructor before participating if you have any questions. If extra credit is awarded and you choose to not participate, the instructor will offer an equitable alternative."
- H4. If you intend to submit to the Travel Management Office for reimbursement purposes make sure you understand what each level of payment confidentiality means ([click here for additional information](#)).

H1. Does this study involve incentives or compensation to the subjects? For example cash, class extra credit, gift cards, or items.

Yes

No [SKIP THIS SECTION]

H2. Explain what (a) the item is, (b) the amount or approximate value of the item, and (c) when it will be given. For extra credit, state the number of credit hours and/or points. (e.g., \$5 after completing each survey, subject will receive [item] even if they do not complete the procedure, extra credit will be award at the end of the semester):

Upon completion of the first phase of the study, participants will be allowed to keep the PoNS™ device they used throughout the first phase if they agree to continue into Phase II, the longitudinal component to the study. If they do not choose to continue into Phase II, they will be asked to return the device. If they choose to withdraw at any point, they will be asked to return the device. After the completion of the 3 year follow-up, participants will be asked to return the device. If, after three years, in the unlikely event that the device is not FDA approved and a participant remains dependent on using the device, researchers will consider extending the study to continue tracking the individual.

H3. If extra credit is offered as compensation/incentive, an alternative activity (which can be another research study or class assignment) should be offered. The alternative activity (either class assignment or another research study) should be similar in the amount of time involved to complete and worth the same extra credit.

NA

H4. If cash or gift cards, select the appropriate confidentiality level for payments (see section notes):

Level 1 indicates that confidentiality of the subjects is not a serious issue, e.g., providing a social security number or other identifying information for payment would not pose a serious risk to subjects.

- Choosing a Level 1 requires the researcher to maintain a record of the following: The payee's name, address, and social security number and the amount paid.
- When Level 1 is selected, a formal notice is not issued by the IRB and the Travel Management Office assumes Level 1.
- Level 1 payment information will be retained in the extramural account folder at UWM/Research Services and attached to the voucher in Accounts Payable. These are public documents, potentially open to public review.

Level 2 indicates that confidentiality is an issue, but is not paramount to the study, e.g., the participant will be involved in a study researching sensitive, yet not illegal issues.

- Choosing a Level 2 requires the researcher to maintain a record of the following: A list of names, social security numbers, home addresses and amounts paid.
- When Level 2 is selected, a formal notice will be issued by the IRB.
- Level 2 payment information, including the names, are attached to the PIR and become part of the voucher in Accounts Payable. The records retained by Accounts Payable are not considered public record.

Level 3 indicates that confidentiality of the subjects must be guaranteed. In this category, identifying information such as a social security number would put a subject at increased risk.

- Choosing a Level 3 requires the researcher to maintain a record of the following: research subject's name and corresponding coded identification. This will be the only record of payee names, and it will stay in the control of the PI.
- Payments are made to the research subjects by either personal check or cash.
- Gift cards are considered cash.
- If a cash payment is made, the PI must obtain signed receipts.

SECTION I: Deception/ Incomplete Disclosure (INSERT "NA" IF NOT APPLICABLE)

Section Notes...

- If you cannot adequately state the true purpose of the study to the subject in the informed consent, deception/ incomplete disclosure is involved.

I1. Describe (a) what information will be withheld from the subject (b) why such deception/ incomplete disclosure is necessary, and (c) when the subjects will be debriefed about the deception/ incomplete disclosure.

NA

UNIVERSITY OF WISCONSIN – MILWAUKEE CONSENT TO PARTICIPATE IN RESEARCH Phase 1 Consent

This Consent Form has been approved by the IRB for a one year period

1. General Information

Study title:

Beneficial and Withdrawal Effects of Cranial Nerve Non-Invasive Neuromodulation on Functional Mobility for Individuals with Traumatic Brain Injury with Multiyear Follow-up: Phase 1

Person in Charge of Study (Principal Investigator):

Study Advisor: Roger O. Smith, Ph.D., OT, FAOTA

Dr. Smith is the director of the Rehabilitation Research Design and Disability (R₂D₂) Center and a professor in the Occupational Science and Technology Department at the University of Wisconsin-Milwaukee.

Primary Researcher: Kati Liegl, B.S.

Ms. Liegl is a graduate assistant at the Rehabilitation Research Design and Disability (R₂D₂) Center and completing her Master's thesis in Occupational Therapy at the University of Wisconsin-Milwaukee.

2. Study Description

You are being asked to participate in a research study. Your participation is completely voluntary. You do not have to participate if you do not want to.

Study description:

This study is interested in studying the immediate and withdrawal effects of a very new rehabilitation approach created at the University of Wisconsin – Madison. The approach uses the same type of treatments to improve balance and walking that you participated in during rehabilitation. However, you will have a small device in your mouth for 20 minutes at a time while you are performing the rehabilitation activities. The device delivers mild electrical stimulation to your tongue. Many people say the stimulation feels like drinking a carbonated beverage. Four people who still have walking problems since their head injury will be in the study.

We think the electrical stimulation helps prepare your brain to learn, especially areas that help control your movements and areas that help your senses work together. We are interested in what happens to your balance and walking. We are also interested in what happens when the intervention stops and how long any changes last. This study hopes to provide another safe option to help therapists treat people with walking or balance problems after they have a head injury.

This study will require a great deal of work and time. We think this study will last five weeks. There is a small chance the researchers may ask you to continue the study for an extra week, but this is not expected to happen unless you cannot come to the lab several days for any reason. During the first, third, and fifth weeks, you will come to the lab every day, Monday through Friday, for about 45 minutes each day. Every day you will be tested on your walking and on Friday you will complete three surveys as well. During the second and fourth weeks, you will come to the laboratory twice a day, once in the morning and once in the afternoon. Each of these appointments will take about 90 minutes for a total of three hours in the laboratory every day during both intervention weeks. During those weeks, you will also use the stimulation device two times in the evening at home.

After the first five weeks, if you would like to continue to use the device, you will be able to participate in a second part to the study. You can decide at the end of the first five weeks if you would like to continue. If you decide not to continue, you will be asked to return the device. For the second part, we will give you general guidelines on how to use the device but you will be using it on your own at your home. We will be available for questions during this time. You will be asked to track your usage of the intervention on a calendar we give to you and return to the laboratory for 90 minute follow-up appointments every six months for the following three years. Again, you can decide if you want to participate in that part of the study after completing the first five weeks. Signing this form does NOT mean you will participate in the second part to the study.

3. Study Procedures

What will I be asked to do if I participate in the study?

If you agree to participate, you will complete activities similar to the rehabilitation you completed after your injury. The main difference is that this study will use a device that stimulates your tongue with small, safe doses of electricity while you are doing the balance and walking activities. In general, the study will last 5 weeks. During the first, third, and fifth weeks, you will be tested every day on a walking test. These visits will be about 45 minutes. At the end of each week you will take the three surveys. During the second and fourth weeks, you will do the same testing, but you will also do training in the lab. The training will be twice per day (Monday through Friday) for 90 minutes in the morning and 90 minutes in the afternoon. The training will be similar to previous rehabilitation you have participated in. The last page of this document shows what you will be doing each day for the study. During the study, we also would like to videotape your walking test. If you decide you do not want to be videotaped, you can still participate in the study. We will use the videotape to have another therapist score the walking test you are completing to make sure the score is accurate.

You will provide your own transportation to the University of Wisconsin Milwaukee or Independence *First* five times a week (Monday-Friday) for five weeks. Parking at UW-Milwaukee will be paid by the researcher but you will not receive payment if you park at Independence *First*. Basically, one week of daily testing only is followed by one week of daily training. This repeats for 5 weeks. You will have one day of testing before starting the 5 weeks in a row. At the first visit, you will be provided an Informed Consent. The Informed Consent will be explained to you and you will get a copy to keep. After having time to read it, and after signing it, you will complete three surveys on your own (the Community Integration Questionnaire, Participation Objective Participation Subjective, and modified Gait Efficacy Scale). You will also be tested using a walking test called the Community Balance & Mobility Scale. This test will be videotaped

if you give us your permission During the first week, you will be tested every day with the walking test. The second and fourth weeks will be training (intervention) weeks and the third and fifth weeks will be withdrawal weeks where once again we test your walking every day and you do not do training.

If you complete the study at Independence^{First}, all the information will be kept as a paper copy and on the disk for the videocamera. This information will be in the possession of the primary researcher at all times. After the completion of each day's training or testing, the primary researcher will take the information directly back to a secured location at UW-Milwaukee.

During the second and fourth weeks, we will train you to know how to take care of and use the device that delivers the mild electrical stimulation to your tongue. This device is called the Portable Neurostimulator (PoNS™). The PoNS™ device is an investigational device and has not yet been approved by the FDA. The intervention we are studying combines the therapy activities similar to those you have already completed in rehabilitation with stimulation of the tongue with the PoNS™ device. Each intervention session during the second and fourth week will include 20 minutes of each training focused on balance, relaxation, and gait. You will use the PoNS™ device while you do the balance and gait activities. The balance activities include things like standing on foam with your eyes closed, or standing on the floor with your feet close together without shoes and with your eyes closed. Gait (walking) activities include things like walking on a treadmill focused on fixing posture or the lengths of each step. Other gait activities might include walking backwards or walking outside on uneven surfaces like the grass. Relaxation training will help you focus on breathing and body awareness while you are sitting. You will complete the trainings in the lab in the morning and in the afternoon. In the evening, you will use the device two more times, each time for 20 minutes while doing activities you learned in the lab. In addition to the training, you will be tested every day using the walking test. At the end of the week, you will also fill out all 3 surveys that you did on the first day.

During the two withdrawal weeks, we do not want you to practice the trainings you learned or use the PoNS™ device. You will be tested using the walking test every day.

During the whole study, we encourage you to write down any changes that you notice that you think are related to the study. This information helps us plan research in the future, and understand your progress.

After the five weeks to finish this study, you will be able to choose if you want to keep using the device by completing the second part to this study. If you do not, you will be asked to return the device. If you do continue with the study, you will return to the laboratory every six months to complete the same test and surveys used on the first visit. Between follow-up visits, you would record how often you use the device by marking a calendar we give you.

Any new findings that may impact your willingness to participate in this study will be reported to you before your next visit to the laboratory and within two days.

4. Risks and Minimizing Risks

What risks will I face by participating in this study?

You will face minimal risks by participating in the study. There is a slight risk of the loss of confidentiality. To reduce this risk, only the primary researcher and study advisor will have

access to information that identifies you. If you complete the study at Independence *First*, the information collected will be taken directly to UW-Milwaukee and secured at the end of the testing or training each day. All information will be stored confidentially on a password protected server that is only accessible to core administrators and the primary researcher. All your information will also be encrypted when it is stored on the password protected server.

There is a slight risk of falling during the walking test and training activities. This risk is no greater than the risk of falling during other standard rehabilitation interventions you may have participated in. To reduce the risk of falling, a trained researcher with a therapy education and background will be with you to make sure the activities are safe and help or steady you as needed. You may be asked to wear a gait belt if necessary to further reduce the risk of falling (the belt will help the researcher hold onto you and help steady you, if necessary).

In the unlikely event that you do fall during your time in the lab, the test or training will stop immediately and the situation will be assessed. If you are injured while at the lab, emergency care will be called. However, you will be responsible for the cost from the emergency care. There is no commitment to provide compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact the Principal Investigator, Roger O. Smith at 414-229-5625 if you believe you are injured or require further information.

In the research with the PoNS™ device and similar older versions, no one has described a negative reaction to the device. You will always be in control of the device and the intensity of the stimulation. If it is ever uncomfortable, you can turn down the intensity, turn off the device or take it out of your mouth at any time. If you experience a negative or uncomfortable reaction, you will stop using the device right away. Then you will meet with the study advisor, primary researcher, and experts in the intervention from Madison to discuss the negative effect and the options for continuing or discontinuing the study.

It is possible that your balance and walking abilities will not get better. This may result in negative emotional reactions. This has not been recorded in previous research.

You may stop participating in this study at any time during the study for any reason. If you choose to stop, you will be asked to return the PoNS™ device.

5. Benefits

Will I receive any benefit from my participation in this study?

Being in this study will add to the research on cranial nerve non-invasive neuromodulation (the intervention created in Madison) used to improve walking ability. What we learn from this study will help make rehabilitation better in the future for people who experience a traumatic brain injury and have balance or walking problems because of the injury. It is important that we study the effects and withdrawal effects of the intervention. Your participation in the study will help this research.

It is possible that your walking will improve during the intervention weeks. You may notice an improvement that lasts through the withdrawal weeks. Some of the people who used the device in the past noticed other positive changes also. If you are interested, you can choose later to participate in the second part to the study.

6. Study Costs and Compensation

Will I be charged anything for participating in this study?

You will not be responsible for any of the costs from taking part in this research study. However, you will be expected to provide your own transportation to and from the research lab without compensation. Parking at UWM will be paid for you.

Are subjects paid or given anything for being in the study?

You will not be paid or given anything when you finish the study. When you finish the study, you will be asked to return the PoNS™ device. If you decide to be in the second phase, you will keep the device until you are finished with the second phase.

7. Confidentiality

What happens to the information collected?

All information collected about you during the study will be kept confidential to the extent permitted by law. We may decide to present what we find to others, or publish our results in scientific journals or at scientific conferences. Information that identifies you personally will not be released without your written permission. All information will be kept on a password protected computer on a secure University of Wisconsin-Milwaukee server. All files and back-up files will be encrypted to further protect the information. Any paper forms will be stored in a locked cabinet in a locked office in the R₂D₂ Center at UW-Milwaukee. If you complete the study at Independence^{First}, your information will be taken directly to this location after the training or testing each day by the primary researcher. Information will be kept for five years after the study for future use. Only the study principal investigator, Roger O. Smith, and primary researcher, Kati Liegl will have access to identifying information. However, the Institutional Review Board at UW-Milwaukee or appropriate federal agencies like the Office for Human Research Protections and the U.S. Food and Drug Administration (FDA) may review this study's records.

8. Alternatives

Are there alternatives to participating in the study?

There are no known direct alternatives available to you other than not taking part in this study. A slightly different alternative may be to speak with your doctor to request more therapy services. It is possible that insurance may pay for therapy services ordered by your doctor. It is also possible that you may be responsible for paying for the extra therapy, depending whether you qualify for additional therapy. Other alternatives not connected to this research study might include Alternative and Complementary Medicine approaches, like yoga, acupuncture, or fitness groups.

9. Voluntary Participation and Withdrawal

What happens if I decide not to be in this study?

Your participation in this study is voluntary. You may choose not to take part in this study at any time. If you decide to take part, you can change your mind at any time and withdraw from the study. You are free to not answer any questions. If you withdraw from the study early, we will ask you to return the PoNS™ device. Researchers may use the information collected to that point. Your decision will not change any present or future relationships with the University of Wisconsin Milwaukee and will not affect any insurance coverage.

10. Questions**Who do I contact for questions about this study?**

For more information about the study or the study procedures or treatments, or to withdraw from the study, contact:

Primary Researcher: Kati Liegl
University of Wisconsin-Milwaukee
Rehabilitation Research Design & Disability (R₂D₂) Center
P.O. Box 413
Milwaukee WI 53201
414-229-6803

Study Advisor: Dr. Roger O. Smith
University of Wisconsin-Milwaukee
Rehabilitation Research Design & Disability (R₂D₂) Center
P.O. Box 413
Milwaukee WI 53201
414-229-5625

Who do I contact for questions about my rights or complaints towards my treatment as a research subject?

The Institutional Review Board may ask your name, but all complaints are kept in confidence.

Institutional Review Board
Human Research Protection Program
Department of University Safety and Assurances
University of Wisconsin – Milwaukee
P.O. Box 413
Milwaukee, WI 53201
(414) 229-3173

11. Signatures**Research Subject's Consent to Participate in Research:**

To voluntarily agree to take part in this study, you must sign on the line below. If you choose to take part in this study, you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read or had read to you this entire consent form, including the risks and benefits, and have had all of your questions answered, and that you are 18 years of age or older.

Printed Name of Subject

Signature of Subject

Date

Research Subject's Consent to Audio/Video/Photo Recording:

It is okay to videotape me while I am in this study and use my videotaped data in the research. Choosing not to be videotaped will not affect my ability to be in the study.

Please initial: ___ Yes ___ No

Principal Investigator (or Designee)

I have given this research subject information on the study that is accurate and sufficient for the subject to fully understand the nature, risks and benefits of the study.

Printed Name of Person Obtaining Consent

Study Role

Signature of Person Obtaining Consent

Date

UNIVERSITY OF WISCONSIN – MILWAUKEE CONSENT TO PARTICIPATE IN RESEARCH Phase 2 Consent

This Consent Form has been approved by the IRB for a one year period

1. General Information

Study title:

Beneficial and Withdrawal Effects of Cranial Nerve Non-Invasive Neuromodulation on Functional Mobility for Individuals with Traumatic Brain Injury with Multiyear Follow-up: Phase 2

Person in Charge of Study (Principal Investigator):

Study Advisor: Roger O. Smith, Ph.D., OT, FAOTA

Dr. Smith is the director of the Rehabilitation Research Design and Disability (R₂D₂) Center and a professor in the Occupational Science and Technology Department at the University of Wisconsin-Milwaukee.

Primary Researcher: Kati Liegl, B.S.

Ms. Liegl is a graduate assistant at the Rehabilitation Research Design and Disability (R₂D₂) Center and completing her Master's thesis in Occupational Therapy at the University of Wisconsin-Milwaukee.

2. Study Description

You are being asked to participate in a research study. Your participation is completely voluntary. You do not have to participate if you do not want to.

Study description:

Because you finished the first part of the study, you are being invited to participate in Phase II of the study. We want to study any additional effects when you use this device over a longer period of time. This is an investigational device and has not yet been approved by the FDA. This part of the study uses the same small device you have been using to stimulate the tongue with mild electrical current and the same training activities that were started in Madison. This study will help us learn how you choose to use the device at home. You will come back to the lab two times each year for three years to complete tests so we can track your progress. We expect that four people who still have walking problems since their head injury will be in the study.

We think the electrical stimulation helps prepare your brain to learn, especially areas that help control your movements and areas that help your senses work together. We are interested in what happens to your balance and walking as well as any other changes you notice. We are also interested in what happens when the intervention stops. Because this is a new intervention, we want to study your walking and balance abilities for three more years. This study hopes to provide another safe option to help therapists treat people with walking or balance problems after they had a head injury.

This study will require you to track how often you choose to use the device as you continue to use it for three years. You can use the device as often as you would like (up to the amount you used it in the first study) or as little as you want. We will give you guidelines on how to use it but you will be using it on your own. We will be available for questions during this time. We will also send you an email every month to remind you to keep writing down how often you use the device. You will also come back to the lab every six months for three years to do the walking test and the same three surveys you did in the first part of the study. Each visit will be to the R₂D₂ Center Laboratory and will take about 90 minutes.

3. Study Procedures

What will I be asked to do if I participate in the study?

If you agree to participate, you will be asked to provide your own transportation to the University of Wisconsin Milwaukee once every six months. Parking at UW-Milwaukee will be paid for you at each of your visits. Each visit will take 90 minutes and you will complete three surveys on your own (the Community Integration Questionnaire, Participation Objective Participation Subjective, and modified Gait Efficacy Scale). You will also be tested by a researcher on a walking test (the Community Balance & Mobility Scale). During the study, we also ask that we can videotape your walking test. If you decide not to be videotaped, you can still participate in the study. We will use the videotape to have another therapist score the walking test you are completing to make sure the score is accurate.

You will also be asked to keep track of how many times per day you choose to use the device. We will give you a calendar for each month, and you will be asked to put an 'X' on the day each time you use the device. On the back of the calendar is a spot you can write down anything that you think is important or notice changing. What you write will help us understand your experience but you do not have to write anything. You will be asked to bring the calendars with you when you come to the lab every six months.

We will send you an email once per month to remind you to use the calendar. We also welcome any questions you have at any time. You do not have to reply to the emails, but you can contact us if you have questions or would like to share your experiences between visits.

Any new findings that may impact your willingness to participate in this study will be reported to you before your next visit to the laboratory and within two days.

4. Risks and Minimizing Risks

What risks will I face by participating in this study?

You will face minimal risks by participating in the study. There is a slight risk of the loss of confidentiality. To reduce this risk, only the primary researcher and study advisor will have access to information that identifies you. All information will be stored confidentially on a password protected server that is only accessible to the primary researcher and study advisor. All your information will also be encrypted when it is stored on the password protected server.

There is a slight risk of falling during the walking test. This risk is no greater than the risk of falling during what you do every day or other standard rehabilitation interventions you may have

participated in. To reduce the risk of falling, a trained researcher with a therapy education and background will be with you. You will be asked to wear a gait belt to reduce the risk of falling, if the researcher feels it is necessary. In the unlikely event that you do fall during your time in the lab, the test or training will stop immediately and the situation will be assessed. If you are injured while at the lab, emergency care will be called. However, you will be responsible for the cost from the emergency care. There is no commitment to provide compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact the Principal Investigator, Roger O. Smith at 414-229-5625 if you believe you are injured or require further information.

In the research with the PoNS™ device and similar older versions, no one has described a negative reaction to the device. If you experience a negative or uncomfortable reaction, you will stop using the device immediately and meet with the study advisor, primary researcher, and experts in the intervention from Madison to discuss the negative effect and the options for continuing or discontinuing the study.

It is possible that your balance and walking abilities will not get better. This may result in negative emotional reactions. This has not been recorded in previous research.

You may stop participating in this study at any time during the study for any reason. If you choose to stop, you will be asked to return the PoNS™ device. At the end of the three years, you will be asked to return the PoNS™ device.

5. Benefits

Will I receive any benefit from my participation in this study?

Being in this study will add to the research on cranial nerve non-invasive neuromodulation (the intervention created in Madison) used to improve walking ability. What we learn from this study will help make rehabilitation better in the future for people who experience a traumatic brain injury and have balance or walking problems because of the injury. It is important that we study any long-term effects of the intervention. Your participation in the study will help this research.

It is possible that your walking will improve over time if you continue to use the device.

6. Study Costs and Compensation

Will I be charged anything for participating in this study?

You will not be responsible for any of the costs from taking part in this research study. However, you will be expected to provide your own transportation to and from the research lab without compensation.

Are subjects paid or given anything for being in the study?

You will be allowed to keep the PoNS™ device during the three years of the study as long as you are personally using it. If you decide to stop using the device, you will be asked to return it to the primary researcher or study advisor. You will not be paid anything to be in the study, but if you park on campus, your parking will be paid for you.

7. Confidentiality

What happens to the information collected?

All information collected about you during the study will be kept confidential to the extent permitted by law. We may decide to present what we find to others, or publish our results in scientific journals or at scientific conferences. Information that identifies you personally will not be released without your written permission. All information will be kept on a password protected computer on a secure University of Wisconsin-Milwaukee server. All files and back-up files will be encrypted to further protect the information. Any paper forms will be stored in a locked cabinet in a locked office in the R₂D₂ Center at UW-Milwaukee. Information will be kept for five years after the study for future use. Only the study principal investigator, Roger O. Smith, and primary researcher, Kati Liegl will have access to identifying information. However, the Institutional Review Board at UW-Milwaukee or appropriate federal agencies like the Office for Human Research Protections and the U.S. Food and Drug Administration (FDA) may review this study's records.

8. Alternatives

Are there alternatives to participating in the study?

There are no known direct alternatives available to you other than not taking part in this study. A slightly different alternative may be to speak with your doctor to request more therapy services. It is possible that insurance may pay for therapy services ordered by your doctor. It is also possible that you may be responsible for paying for the extra therapy, depending whether you qualify for additional therapy. Other alternatives not connected to this research study might include Alternative and Complementary Medicine approaches, like yoga, acupuncture, or fitness groups.

9. Voluntary Participation and Withdrawal

What happens if I decide not to be in this study?

Your participation in this study is voluntary. You may choose not to take part in this study at any time. If you decide to take part, you can change your mind at any time and withdraw from the study. You are free to not answer any questions. If you withdraw from the study early, we will ask you to return the PoNS™ device. Researchers may use the information collected to that point. Your decision will not change any present or future relationships with the University of Wisconsin Milwaukee and will not affect any insurance coverage.

10. Questions

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For more information about the study or the study procedures or treatments, or to withdraw from the study, contact:

Primary Researcher: Kati Liegl

University of Wisconsin-Milwaukee
Rehabilitation Research Design & Disability (R₂D₂) Center
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Milwaukee WI 53201
414-229-6803

Study Advisor: Dr. Roger O. Smith
University of Wisconsin-Milwaukee
Rehabilitation Research Design & Disability (R₂D₂) Center
P.O. Box 413
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414-229-5625

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The Institutional Review Board may ask your name, but all complaints are kept in confidence.

Institutional Review Board
Human Research Protection Program
Department of University Safety and Assurances
University of Wisconsin – Milwaukee
P.O. Box 413
Milwaukee, WI 53201
(414) 229-3173

11. Signatures

Research Subject’s Consent to Participate in Research:

To voluntarily agree to take part in this study, you must sign on the line below. If you choose to take part in this study, you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read or had read to you this entire consent form, including the risks and benefits, and have had all of your questions answered, and that you are 18 years of age or older.

Printed Name of Subject

Signature of Subject

Date

Research Subject’s Consent to Audio/Video/Photo Recording:

It is okay to videotape me while I am in this study and use my videotaped data in the research. Choosing not to be videotaped will not affect my ability to be in the study.

Please initial: Yes No

Principal Investigator (or Designee)

I have given this research subject information on the study that is accurate and sufficient for the subject to fully understand the nature, risks and benefits of the study.

Informed Consent

IRB Protocol Number:

Version:

IRB Approval Date:

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Printed Name of Person Obtaining Consent

Study Role

Signature of Person Obtaining Consent

Date