Extending taVNS Paired With Infant CIMT Into a Home-Based Setting: Technology Expansion Requisite for a Randomized Trial

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1.0 Objectives / Specific Aims

Newborns who are born premature or suffer brain injury at birth are at risk for motor problems. The common motor skills of reaching and grasping that infants have to learn can be weaker on one side of the body, depending on the site of the brain injury. These skills are practiced with an occupational therapist, to help the infant strengthen these skills. The gold standard rehabilitation intervention to address one sided motor weakness is Constraint Induced Movement Therapy (CIMT). During CIMT interventions, an infant wears a removable splint or puppet on their stronger hand while the therapist engages the infant in various activities targeted to improve functioning of the weaker side. CIMT encourages infants to move the weaker arm and hand and strengthen the circuits in the brain involved with movement. Even with the high intensity therapy program of CIMT, it takes between 40-120 hours total treatment time for most infants to improve their motor skills. We hope to improve motor outcomes by pairing CIMT with technology shown to improve motor functioning due to brain damage.

The purpose of this study is to evaluate the safety and effectiveness of using Electromyography (EMG) muscle sensors to trigger a non-invasive brain stimulation technique, called Transcutaneous auricular Vagus Nerve Stimulation (taVNS) during CIMT in order to improve motor outcomes for this intensive rehabilitation intervention.

Explanation of technology:

- **Electromyography (EMG) Sensors:** EMG sensors are adhesive electrode sensors that detect electrical activity in a muscle, in other words sensors that detect if a muscle is "on or off". In this study we will place EMG sensors over key muscles in the shoulders and trunk to automatically detect when an infant is reaching or using their trunk to work on activities like sitting or rolling in therapy. When muscles are activated, it will trigger taVNS stimulation. Pairing nerve stimulation with movement may boost rehabilitation outcomes when paired with motor activities in infants and adults post stroke or brain injury.

- **Transcutaneous auricular Vagus Nerve Stimulation (taVNS):** taVNS, provides low level electrical stimulation (<2.0 mA) to the vagal nerve via an electrode placed on the ear. A course of daily vagal nerve stimulation has been shown to be safe and to help the brain learn motor tasks in adults and in our study of infants with brain injury or prematurity, without side effects. Nerve stimulation has also been used in neonates to decrease pain and improve motor function after nerve injury at birth. With electrodes on the child's left ear, the transcutaneous electrical nerve stimulator device will deliver short treatments of small electric pulses while he or she is undergoing CIMT with a therapist. These devices are FDA approved for pain management on muscles, and FDA-cleared and widely available for purchase online without a prescription for home use in adults and children. We will use this FDA-approved technology to stimulate the vagus nerve and brain pathways involved in motor control.

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The FDA has approved transcutaneous electrical nerve stimulation (TENS) therapy for pain management. TENS requires placing electrodes directly on the skin of a specific part of your body. Small pulsed electrical currents are then delivered to these electrodes, which stimulate the underlying muscles and nerves. taVNS is a specific use of this FDA approved therapy, and is just another name for TENS therapy on the ear. We think it may have different effects than TENS on muscles, because we can stimulate a large nerve, called the vagus nerve, in the ear. This nerve connects to the brain and is important in many functions. In animals with brain injury, stimulation of the vagus nerve combined with specific motor training helps repair the motor areas of the brain. In adults and infants, taVNS improves motor function, when paired with a motor task. Using taVNS in infants to improve motor skills is experimental, even though the TENS device is cleared by the FDA.

Rationale for Pairing EMG triggered taVNS with CIMT.

Constraint Induced Movement Therapy (CIMT) is the gold-standard in pediatric rehabilitation, but it is time intensive (2-5h per day) and unfeasible for many families if delivered in a clinic setting. Therefore, we want to maximize functional benefits for the intervention.

We will test whether EMG muscle sensors can be used to pair experimental taVNS with active movement while the child participates in 40 hours of CIMT rehabilitation treatment. CIMT encourages the infant to move his or her weaker arm and hand better and strengthen the circuits in the brain involved with movement.

The data in animals and humans support the premise that both cervically-implanted and transcutaneous auricular VNS (non-invasive stimulation method using an electrode on placed on the ear) paired with motor rehabilitation improve functioning.[18--32] In rats, cervically-implanted VNS paired with movement led to a doubling in size of the primary motor cortex associated with the movement.[18]

Our group is the first to show the benefit of using non-invasive taVNS paired with a motor task of bottle-feeding in infants with brain injury and oromotor feeding failure. We also recently successfully delivered 40 hours of CIMT paired with taVNS to a former premature infant, now 11 months old, with significant brain injury and left-sided hemiplegia enrolled in our NM4R-funded feasibility trial. The infant had little to no spontaneous movement of the left arm, elbow or hand prior to study participation, in spite of weekly physical and occupational therapy and home exercises with the mother. The infant made rapid progress significantly passing expected outcomes expected for CIMT alone. By the 3rd & 4th weeks of therapy mom reported he was regularly engaging in bimanual play at home.

After training in taVNS, the therapist was able to deliver taVNS using a manual trigger and engage the infant in CIMT. Manually triggering taVNS for every active movement seen during an intensive intervention is mentally taxing for the therapist. In this study, we want to trial use of EMG sensors

to trigger stimulation. Placing EMG sensors over key muscles in the shoulders and trunk we allow us to automatically detect when an infant is reaching or using their trunk to work on activities like sitting or rolling. By using EMG sensors we should be able to pair stimulation with movements reducing the burden on the therapist and allowing them to focus on facilitating a high quality treatment session. Automating the stimulation would make taVNS-paired CIMT more achievable in the home-based CIMT programs. Home-based delivery of CIMT is considered best practice for pediatric clients so families can be fully engaged, burden for families is reduced, and new skills can easily transfer to the natural environment for better carry over of treatment.

Qualifications

We have a unique collaboration of experts in brain stimulation, pediatric brain injury, translational clinical science and pediatric occupational therapy in this pilot project, and we are one of the few groups able to rapidly translate this neuromodulatory modality into home-based CIMT services. Refining the treatment protocol for home-based taVNS+CIMT and trialing incorporation of reliable taVNS triggering by this device we will provide us strong data to submit a grant for a randomized trial of home delivered taVNS+ CIMT in infant hemiplegia.

Study Aims

Aim 1: Investigate the feasibility of incorporating automatic triggering of the taVNS device using EMG sensors. *Rationale:* Manual taVNS triggering is mentally taxing for a therapist providing intensive, CIMT intervention. Movement based triggering would decrease the mental effort for using taVNS allowing the therapist to focus more on the treatment session. *Aim specific methods:* We will systematically test key muscle groups to see if EMG can be used to trigger taVNS stimulation at least 75% of the total time for active infant arm and trunk movements during CIMT. The first 2 participants will be completed in clinic to allow for updates to EMG system real time. After the first 2 participants complete the study we will trial the EMG system in the home setting for Aim 2.

Aim 2: To generate proof of concept evidence demonstrating ability to provide high fidelity CIMT+taVNS treatment in a home-based setting in 3 infants. *Rationale:* The strongest level of evidence exists for delivery of pediatric interventions in home-based settings. We need to show evidence that CIMT +taVNS can be delivered effectively in the home and not just in a research clinic. *Aim Specific Methods:* We will videotape CIMT therapy sessions while the therapist is delivering taVNS in the home with EMG triggered taVNS and randomly score 20% of weekly session for CIMT treatment fidelity with the published CIMT Fidelity Instrument. Home based fidelity will be completed with the last 3 participants.

Project Relevance: Home-based constraint induced movement therapy (CIMT) is the gold standard treatment to facilitate arm and hand recovery after pediatric stroke, but it requires a large investment of time and energy from therapists and the family. Non-invasive brain stimulation (taVNS) is a promising new technology that may amplify the treatment effect of

therapy treatment. Combining home-based CIMT & taVNS may provide families a better return on investment in terms of their child's functional gains from therapy services. This technology development pilot project will address important system modifications to automate pairing of active movement with taVNS delivers. This automation is needed to decrease the burden of pairing taVNS with CIMT and increase likelihood of clinical translation into home-based settings

2.0 Background

A. SIGNIFICANCE Preterm birth and complications in term births result in increased risk for intraventricular hemorrhage, global hypoxia-ischemia (HIE), arterial stroke, and neuroinflammation with white matter injury in newborns[1-5]. Perinatal CNS injuries may significantly disrupt motor circuit development resulting in life-long deficits, such as cerebral palsy (CP). Early targeted therapy interventions for high-risk infants may improve neurological outcomes by taking advantage of early critical windows for neuroplasticity[1,5].

Intensive interventions, such as constraint induced movement therapy (CIMT), are designed to ameliorate early motor predecessors of CP in at-risk infants[6-12]. Standard pediatric rehabilitation CIMT programs use high-dose rehabilitation to reinforce activity-dependent neuroplasticity[6,7,9]. Multiple rigorous CIMT studies show functional improvement in motor-impaired children after 60-120h of treatment. Yet it is difficult for many families[10] to complete even the minimally effective dose of 40h[11] (2 hours/day sessions for 4 weeks). Frequently families will go to great lengths to participate in any type of CIMT programming- traveling out of state and staying in hotels so their child can participate in a 1-week group based CIMT program for older children. But this is not possible for many families that lack extensive social and financial resources. **Therefore, it is critical to find ways to make CIMT accessible for all families and maximize the return on investment for the child.**

One way of increasing functional gains with less time and resources, may be pairing CIMT with non-invasive vagus nerve stimulation (taVNS). Recent research suggests that even with significant brain injury, neuromodulation via vagus nerve stimulation (VNS) delivered during a motor task can harness activity-dependent plasticity and lead to improved functional outcomes[13-17]. **Encouraged by exciting pilot data, we hypothesize that brain stimulation via taVNS delivered during CIMT will boost cortical plasticity of neural circuits, resulting in better functional outcomes in a shorter time**.

Our team is passionate about developing technology that improves functional outcomes AND can be readily translated into practice. This team was previously awarded pilot funding from NM4R to develop a taVNS device for testing safety and feasibility of pairing taVNS and CIMT. Initial results are encouraging (see data in section C1). However, the current technology requires the therapist to manually trigger the taVNS device, distracting from the therapy and necessitating additional support personnel. This therapist triggered setup will not work in the home. *The goal of this technology development project is to refine how the device is triggered, enabling the CIMT therapist to deliver taVNS & CIMT in the home-based setting. Translation of this technology into*

the home is critical for successful implementation of a larger effectiveness clinical trial, as is being done in the IAQUIRE trial (NCT3910075). *It is also essential for removing barriers of subsequent translation into practice*.

B. INNOVATION There is a growing body of evidence indicating VNS may amplify the benefits of rehabilitation interventions; this is now FDA approved for adult stroke recovery[14,15,18-20]. Few studies have investigated combining neuromodulation and evidence-based pediatric intensive therapies such as CIMT, and then only in older children with established CP[21-23]. We propose using taVNS paired with CIMT, in 6–18 month-old infants with unilateral weakness to maximize neuroplasticity in the earliest developmental window. Our team is currently conducting a pilot study testing the feasibility of pairing CIMT and taVNS in infants with hemiplegia, with encouraging results. **Based on our experience in our current taVNS and CIMT pilot study, EMG-triggered automation should greatly increase the likelihood of future clinical translation by 1) decreasing the pre-therapy training required for the therapist, 2) decreasing the mental and physical demands placed on the therapist, and 3) making treatment translatable to the home environment with a single CIMT therapist.**

Our group is pioneering taVNS in infants. We designed and instituted using noninvasive taVNS paired with a motor task of bottle feeding in infants with feeding failure[15,16]. We have expanded this to include pharmacologic therapy with taVNS in infants refractory to standard taVNS-paired feeding. We have seen exciting results in these studies of taVNS to improve bottle feeding for infants in the NICU (preliminary results in section C). With our unique collaboration of experts in brain stimulation, pediatric translational clinical science and pediatric occupational therapy, we have a multidisciplinary team that can rapidly translate this neuromodulatory modality in infants with hemiplegia undergoing CIMT treatment. Our team has extensive experience with taVNS technology development and translation of the technology into clinic settings (George, Summers, Jenkins, Badran), as well as innovative and experienced CIMT therapists (McGloon, Coker-Bolt). The proposed technology development project is an exciting innovation for treatment of perinatal acquired brain injury. **We aim to provide a greater return on investment for intensive CIMT interventions while improving equitable care by improving ability to access this promising treatment combination in the home-based setting.**

C. APPROACH

C1 Preliminary data We have significant experience from our open-label pilot trial of taVNS-paired feeding in infants who were refractory to standard of care feeding interventions and were slated to receive a G-tube[15].

C1.1 taVNS-paired Feeding study: Treatment Protocol: We deliver taVNS pulses via a left ear electrode at 25Hz, pulse width 500µsec at 0.1mA< Perceptual Threshold (PT). Perceptual threshold is determined by increasing stimulation level by 0.1 mA until there is some indication the infant perceives the stimulation. Therapists and the parent watch for signs of perception: facial grimace, vocalization, bringing hand to the ear, turning the head toward that ear. Once Perceptual threshold (PT) is determined stimulation is decreased by 0.1mA to stay below

perceptual level. If at any point during the treatment it seems as if the infant is perceiving the stimulation (reaching to ear, grimace, etc) a break is taken and then PT is retested to determine if stimulation level should be decreased. taVNS treatment is paired with suck-swallowing during 1 (n=15) or 2 (n=18) oral feeds/day, for 2-3 wks. Results: Efficacy outcomes: 19/35 (54%) infants destined for G-tube attained full oral feeds with taVNS-paired feeding in a mean of 2 weeks or less. We showed a dose response with twice vs once daily treatments in the increase of daily po feeding volumes (F,8.05, p=0.01) & faster time to full po feeds (p<0.05). In secondary outcomes, diffusion kurtosis imaging before and after taVNS treatment, showed greater white matter plasticity changes in fractional anisotropy (FA) and white matter complexity for Responders versus Non-Responders in corpus callosum and external capsule, per week of development. Safety outcomes: We observed no bradycardia (HR<80bpm 5sec), no skin irritation. Persistent increase in discomfort scores (NIPS >3) occurred in only 3/228 sessions (1.3%) resolving with decreasing current. *In summary, our first-in-human neonate and infant pilot trial of taVNS paired with an oromotor task of bottle feeding, using our custom taVNS system, showed safety and feasibility, and achieved encouraging results in >50% of infants slated for G-tube achieving full oral feeds in 2 weeks.*

C1.2 CIMT+taVNS Ongoing Safety & Feasibility Pilot

Pediatric CIMT trained therapists provided 40 hours of CIMT paired with taVNS treatment at 0.1mA<Perceptual Threshold (PT) over 4 consecutive weeks. Infant's motor abilities are tested prior to therapy start, immediately after the 4 weeks of therapy and again 3 months post treatement. Primary Outcome: QUEST- an assessment of quality of arm/hand movement in infants & children with CP.

Figures 1 & 2. CIMT therapist assists infant's trunk control while the trigger button is attached to her hand with flexible wrap (red arrow). taVNS device is Velcro attached to the infant's back (green arrow). The arm with better motor skill is immobilized with red flexible wrap and a splint.

RESULTS: We have completed full study procedures for 1 infant. Two other infants have completed pre-assessments and the 40 hours of treatment intervention but have not completed the 3 month follow-up. All 3 infants completed the full intervention with no adverse events. For the first infant, overall, progress was better-than-expected using Goal Attainment Scaling (change 28.33 ± 9.83, p <0.001). At baseline the infant showed little spontaneous use of his left arm, but mom reported he was consistently engaged in bimanual play at home after 4 weeks of combined taVNS-CIMT therapy. Significant improvements were seen on the QUEST in Dissociated Movement (Pre: 43.75, Post 84.38, **Δ=40.63** vs expected Δ=5.2 with CIMT alone[10]) and Grasping (Pre:11.12, Post: 29.62, **Δ=18.5** vs expected Δ =11.1 with CIMT alone[10]). At 3-month follow-up Dissociated Movement scores were maintained (Post 84.38, Follow-up 85.94) and Grasp scores continued to improve (Post 29.62, Follow-up 37.02).

C1.3 Other Achievements that impact this proposal: We recently received FDA Breakthrough Device designation for the BabyStrong device, similar to the system proposed in this application. Our phase I STTR early RCT with this infant taVNS system is currently being funded through an NICHD STTR award. Our infant taVNS feeding data, our early FDA breakthrough

device development for young infants, and other promising studies of taVNS in adults, all support the development of this neuromodulatory technique in infants with significant hemiplegia after perinatally acquired brain injury.

3.0 Intervention to be studied

General Methods for home-based delivery of taVNS +CIMT The goal of this discovery pilot project is to further develop the technical aspects of taVNS+CIMT delivery so that it is practical for delivery by a CIMT therapist in a home-based setting. This is essential to prepare for a treatment effectiveness study, which by necessity must be home-based because of the minimum 40-hour time commitment. First, we will use EMG sensors to automatically trigger the taVNS device, with the goal of decreasing the burden of treatment for the therapist. We will place the EMG sensors on major muscle groups on the shoulder and trunk and refine placement as needed to show that EMG-triggering can accurately and effectively trigger stimulation for 75% of total time spent in active movements. The therapist will still be able to manually trigger for other targeted behaviors (such as grasping). Once our placement of sensors has been tested and meets this designated threshold, the EMG-triggered system will be tested in home-based CIMT treatment.

The therapists providing the CIMT treatment are part of the study team. They have received specialized training in CIMT and the delivery of taVNS. These therapists were also a part of our original CIMT & taVNS study described above in section C1.2. They were part of the team who suggested the modifications of using EMG sensors to automate stimulation.

C2.1.1Inclusion Criteria: Five 6–18 month-old infants, with hemiplegia/motor asymmetry qualifying for CIMT, Gross Motor Function Classification System (GMFCS) level I-IV, ability to maintain sitting position for 5 minutes with moderate assistance. **Exclusion Criteria**: Non-English literate parents, GMFCS level V, severe motor impairment/ quadriplegic involvement; uncorrected blindness or deafness, cardiomyopathy. Infants with cardiac issues will be cleared by cardiology before beginning treatment.

C2.2 Aim 1: Investigate the feasibility of incorporating automatic triggering of the taVNS device using EMG sensors. *Rationale:* Manual taVNS triggering is mentally taxing for a therapist providing intensive CIMT intervention. Movement based, EMG-triggering should decrease the overall burden allowing the therapist to provide high-quality CIMT. Automation may improve pairing of stimulation and motion instead of relying on the therapists to remember to activate/terminate stimulation. It may also decrease the number of personnel required. Using EMG sensors to track every motion would require extensive set-up and complicate treatment by increasing the wires the therapist must manage. Therefore, *we aim to use EMG to selectively target key muscle groups.*

C2.2.1 Models of pairing stimulation to motor activation Direct pairing of stimulation to movement is most effective for functional outcomes[14]. In adult studies therapists manually trigger stimulation for discrete motions that target movement impairments[13,20]. Infant therapy sessions cannot be setup as a series of discrete movements because infants cannot follow directions, have short attention spans, and are only beginning to develop isolated arm movements. In fact, the kinematic and EMG profiles of young infants' reaching indicate that

healthy infants do not show discrete reaching motions indicated by modulation of EMG amplitude until 18 months[25]. Variability is a key element of infant motor development as infants continually trial new movement pattern combinations as they refine skills and learn to adapt movements to match the demands of new environments[26]. Infant reaching kinematic profiles instead appear **more similar to continuous motions and multistep movements**[27]. While this seems like a challenge for automation, it may actually simplify automation, since we want to pair taVNS stimulation with active motor planning and execution of general reaching and dynamic trunk control and do not need to specifically target one motion. *Therefore, we only need to target a few key muscle groups that are consistently activated with immature reaching patterns of young infants.*

C2.2.2 Targeted Muscle Groups We aim to automate 75% of stimulation time without significantly increasing the burden of system set-up/treatment delivery. We will use 2 sets of EMG sensors placed on the muscle groups activated in the vast majority of reaching and dynamic balance tasks.

- Reaching- Immature reaching in infants is initially driven by the biceps and triceps[28,29]. As targeted reaching improves there is an increased use of the deltoids and upper trapezius as prime movers. Depending on the age/ability of the child we will target biceps brachii or anterior deltoid[28,29].
- Trunk control- EMG literature related to development of dynamic sitting balance indicates that thoracic level paraspinal muscles are most involved with emerging sitting balance and transitions to lumbar paraspinal activation as infants progress to more independent sitting balance[28-30].

C2.2.3 Outcome measures for EMG automation taVNS stimulation is most effective when directly paired with active movements. Infant movement kinematics are characteristic of continuous movements rather than discrete movements. Since motions are not clearly discrete, we cannot count the number of stimulations and movements. Instead, a second therapist will record the time that the infant is actively engaged in movement tasks and compare that to the total time of taVNS stimulation, recorded by data acquisition modules in our taVNS set-up. One therapist will be delivering CIMT, a second therapist will be recording active movement time. For the first 2 participants, treatments will be completed in the research lab. This will allow the full team to be present, making sure that EMG triggered stimulation is occurring at the same time as active movement (the screen turns green when stimulation is on). If stimulation is not being delivered during active movement, modifications will be made to the system (e.g. changing amplification threshold for triggering, adjusting sensor location, etc). If total stimulation time is within 75% of total active movement time for therapy sessions in the first 2 infants, then we will transition CIMT delivery to the home-based setting for the final 3 infants.

C2.1.2 Treatment Delivery: CIMT-trained therapist with assistance from a research assistant will deliver CIMT for 40 hours (2 hours/day, 5 days/week for 4 weeks) +taVNS delivered via the BabyStrong (BS) system, (Soterix taVNS electric pulse generator unit & Neolead® electrodes).

1) Hydrogel electrodes are placed in front of tragus and inner tragus/cymba chonchae, securing the wires behind head with tape. taVNS unit is attached to the baby using Velcro cummerbund (Fig.1, 2).

2) EMG electrodes will be placed on the shoulder (biceps/deltoid m) and on the trunk (paraspinus m) and connected to the taVNS unit via a wired interface.
3) CIMT and BSL therapists establish perceptual threshold (PT) daily, increasing slowly, until infant shows signs of tingling sensation. TaVNS is delivered at 0.1mA<PT, 500µsec, 25Hz, during each CIMT session, timed with movements of the weaker arm /trunk.
4) A CIMT therapist will deliver CIMT and use the manual trigger if needed for hand movements, while a second 'recording' therapist will record the active movement time. The Data Acquisition (DAQ) interface will record the amount of stimulation time and intensity from both EMG and manual triggering.
5) Good, moderate or poor impedance is constantly displayed on the taVNS unit. With poor contact, a beep sounds, and the electrode is adjusted.
6) Parent and OT will answer weekly questionnaire to assess their perception of ease of use, infant tolerance, and any recommendations for improvement of taVNS system or delivery.

4.0 Study Endpoints

Primary Research Question: Can taVNS stimulation be automatically triggered during 75% of the total time for active infant arm and trunk movements during CIMT? *Primary Outcome measure:* Percentage of treatment sessions where total stimulation time was 75% of total active movement time.

Limitations and alternative approaches: *Trialing EMG system:* We will trial the EMG sensor system first with two healthy infants in the CHP laboratory setting to trouble shoot set-up and connection issues. The BSL and CIMT team will make any necessary modifications to the EMG-taVNS set-up. *Comparing total movement time to total stimulation time does not ensure stimulation is being provided at the appropriate time*: The stimulation device changes color when stimulation is being provided. Therefore, a second 'recording' therapist can monitor if the screen is green('on') when also recording active movement.

Aim 2: To generate proof of concept evidence demonstrating ability to provide high fidelity CIMT+taVNS treatment in a home-based setting in 3 infants. We will have a second therapist videotape CIMT therapy sessions while the CIMT therapist is delivering taVNS in the home with EMG triggered taVNS. We will randomly score 20% of sessions for CIMT treatment fidelity with published CIMT Fidelity tool. This aim will be completed with the final 3 participants after EMG set-up is finalized with first 2 participants.

Secondary CIMT+taVNS feasibility outcomes: Ability of therapist to operate taVNS easily and successfully by earning a "meet or exceed" score (3 or 4) on random therapy sessions by CIMT Fidelity Instrument. Ability of infant to tolerate wired ear electrode while remaining securely in place during sessions.

Secondary CIMT +taVNS efficacy outcomes: Change in the functional motor outcomes pre and post intervention on the *Quality of Upper Extremity Skills Test (QUEST)*

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5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria: Five 6–18 month-old infants, with hemiplegia/motor asymmetry qualifying for CIMT, Gross Motor Function Classification System (GMFCS) level I-IV, ability to maintain sitting position for 5 minutes with moderate assistance.
Exclusion Criteria: GMFCS level V, severe motor impairment/ quadriplegic involvement; uncorrected blindness or deafness, cardiomyopathy.

6.0 &7.0 Number of Subjects and Setting

We will enroll up to 5 infants. The first two infants will complete all study intervention procedures in the pediatric occupational therapy lab (151 Rutledge Ave Building B). This will allow for monitoring by the whole team and minor modifications to be made to the set-up (adjusting placement of EMG sensors, adding Velcro to keep wires out of the way when reaching, etc). Image from on-going taVNS +CIMT study (without EMG triggering).

This new study should only require minor changes to the set-up (adding wires for EMG muscle sensors). After completing 2 infants in the lab which should provide more than enough opportunity to modify set-up issues. The remaining 3 participants will complete study interventions in their home. A specially trained pediatric therapist will deliver all treatment sessions. A second study team member will also accompany the therapist to assist with therapy, video tape sessions, and monitor the infant.

Figures 1 & 2. CIMT therapist assists infant's trunk control while the trigger button is attached to her hand with flexible wrap (red arrow). taVNS device is Velcro attached to the infant's back (green arrow). The arm with better motor skill is immobilized with red flexible wrap and a splint.

8.0 Recruitment Methods

We have IRB approval for two pilot studies (#67997, #103800) in preterm and term stroke/HIE infants with taVNS paired with feeding using similar taVNS study procedures as proposed in this application. The taVNS system has a non-significant risk device designation from MUSC's IRB in these two pilot trials.

Dr. Jenkins will screen for infants in the nursery with known brain injury that will likely lead to hemiparesis or weakness, such as perinatal arterial stroke, HIE, severe IVH, PVL or cerebellar infarct, regardless of sex or race. The clinical team will inform the parents of the potential to

participate in the study. Dr. Jenkins will then explain the study to the parents and give them contact information if they are interested, to initiate screening and consent procedures when their infant reaches 6-8months of age. Infants are also referred directly to Dr. Coker-Bolt and McGloon specifically for CIMT from a wide region of the southeast. Because some parents travel great distances to get these services, we may obtain referrals from other care providers out of our region. We will perform phone screening and obtain Econsent prior to patient arrival for patients whose parents cannot meet in person prior to the first treatment session, to be able to get services fully prepared for the visit. We will use the approved REDcap system to obtain consent. Dr. Jenkins or other approved study personnel will go over the entire consent document on the phone with the parent to ensure comprehension and to confirm identity. Parent will be given a copy of the completed, signed consent form in person or by email or fax.

Volunteers of all ethnicities and racial categories will be accepted into this study protocol. No preference will be given based on race, gender or ethnicity. Young infants who had perinatal complications leading to perinatally acquired brain injury may be considered vulnerable populations and are the target of this proposal.

The parents of infants who present for CIMT are highly motivated, and willing to commit to the time and effort commitment for CIMT. Most of the study procedures occur during the active treatment period. Therefore, we anticipate >95% retention to completion of the immediate outcome measures. For the 3 months follow-up assessment, we will call every month to discuss infant progress with the mother/caregiver. All of these infants will also have regular developmental follow-up in MUSC's or other high-risk clinic, and we will collect this data with parent consent, though it is not part of the primary or secondary outcomes for the phase I trial.

9.0 Consent Process

Drs. Jenkins, Coker-Bolt, or McGloon (PI and Co-Investigators) will explain the study to these parents by phone or conference call and obtain written informed consent when they and their infants present to the Occupational therapy department for CIMT. Based on our 87% consent rate in the pilot taVNS-feeding study, and the ready parental acceptance of taVNS, we anticipate no significant parental concerns that would impact enrollment. We will not have a Spanish language consent.
We will perform phone screening and obtain eConsent prior to patient arrival for patients whose parents cannot meet in person prior to the first treatment session, to be able to get services fully prepared for the visit. We will use the approved REDcap system to obtain consent. Dr. McGloon or other approved study personnel will go over the entire consent document on the phone with the parent to ensure comprehension and to confirm identity. Parent will be given a copy of the completed, signed consent form in person or by email or fax.

10.0 Study Design / Methods

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Overall Study Design: The goal of this discovery pilot project is to further develop the technical aspects of taVNS+CIMT delivery so that it is practical for delivery by a CIMT therapist in a home-based setting. This is essential to prepare for a treatment effectiveness study, which by necessity must be home-based because of the minimum 40-hour time commitment. First, we will use EMG sensors to automatically trigger the taVNS device, with the goal of decreasing the burden of treatment for the therapist. We will place the EMG sensors on major muscle groups on the shoulder and trunk and refine placement as needed to show that EMG-triggering can accurately and effectively trigger stimulation for 75% of total time spent in active movements. The therapist will still be able to manually trigger for other targeted behaviors (such as grasping). Once our placement of sensors has been tested and meets this designated threshold, the EMG-triggered system will be tested in home-based CIMT treatment.

This study will determine the feasibility of using EMG sensors to trigger taVNS stimulation paired with CIMT therapy in n=5, 6-18month old infants with hemiplegia after perinatally acquired brain injury. We will measure the effect of active taVNS paired with 40 hours of CIMT on infant motor skills before and after treatment over a month, and follow up the motor skills over 3 months. All infants will receive active taVNS treatment. CIMT treatment is a non-research procedure, and motor and developmental testing are non-research procedures. taVNS is a research procedure. CIMT sessions will be videotaped, to measure the fidelity of CIMT delivery while the therapist is delivering taVNS to determine feasibility.

The alternative treatment is the usual and customary occupational therapy services. If parents wish, they may pursue CIMT therapy with local therapists, but there are very few qualified therapists in the area. Also, although CIMT is considered a gold standard intervention, it is often not covered by insurance due to the time intensity required.

We will monitor for and mitigate following risks are present with this study: Risk of skin irritation, risk of discomfort, risk of slightly decreased heart rate, and risk of loss of confidentiality.

Risk of skin irritation: we will monitor the skin on the inner aspect of the left ear before and after each session, and will switch to the right ear if redness is present, and decrease the stimulation if redness persists.

Risk of discomfort: We will protect against the risk of discomfort by close monitoring. We will use the mother's perception of infant discomfort and infant signs of discomfort to determine the perceptual threshold, and then treat at 0.1mA less than this level of perception. If any infant seems to be in discomfort during the CIMT taVNS session, we will decrease the microcurrent by 0.1mA, as in our feeding taVNS trial in infants. We will use facial expression change, fidgety movements and infant vocalization as signs of behavioral discomfort, to indicate need for decreasing the microcurrent during the taVNS session.

We will not continuously monitor heart rate during the taVNS session, as our extensive HR data in infants show no bradycardia and no decrease in HR beyond 60 seconds after starting stimulation.

Risk of loss of confidentiality: We will check the infant's medical records to gather the following information: gestational age at birth, ventilator support, head ultrasound and MRI results, bottle feeding, infection, neonatal condition during labor and delivery, infant's treatments and conditions, and developmental progress.

We will assign study numbers to each participant, keep CRF and consent forms in locked offices. Database files with names and contact information will be password protected and stored on the MUSC Pediatric server. All other data files related to this study will be identified by participant number only, without link to standard identifiers. We will publish the aggregate data only.

11.0 Specimen Collection and Banking

Videotapes will be stored for future use, by Drs. Coker-Bolt and McGloon in a password protected file on the pediatric server, behind MUSC's firewall Future use will include education and teaching sessions and in presentations to describe the combined CIMT and taVNS treatment. They will be deidentified as much as possible although the therapist may use the infants name during CIMT. Only Drs. Coker-Bolt, McGloon and Jenkins and study personnel will have access to subject identities. Only coded identifiers will be used to store and linked to videotapes. If parents wish to withdraw the infant videotapes at any age prior to 18 years, they may request to do so in writing, and withdraw any future use of the child's videotape. Videotapes will not be released to other parties not directly involved in research.

12.0 Data Management

Analysis and Statistical plan: We will compare the change in score on functional measures between CIMT+ taVNS via repeated measures ANOVA from pre- to immediately and 30 days post- treatment via ANOVA. Power analysis on primary outcome is not valid with 5 participants. However, for reference in infants treated with 60 vs 120h intensive CIMT[8], the QUEST grasp mean changed from 4.50±2.6 to 5.25±3.1 with 3h/day CIMT (Δ=0.75), versus 4.14±2.6 to 5.73±3.0 with 6h/day CIMT (Δ=1.59). We estimate 40h of CIMT+taVNS, 2h/day CIMT+taVNS will be similar to 3h CIMT, Δgrasp =0.75.[8]

Keeping Data Confidential: We will assign study numbers to each participant, keep CRF and consent forms in locked offices. Database files with names and contact information will be password protected and stored on the MUSC Pediatric server. All other data files related to this study will be identified by participant number only, without link to standard identifiers. We will publish the aggregate data only.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Data and Safety Monitoring Plan

Title: Extending taVNS Paired with Infant CIMT into a Home-Based Setting: Technology Development Requisite for a Randomized Trial
PI: Kelly McGloon

The participants who receive active taVNS involved with this proposal will be infants whose participation is agreed to by their parent/guardians in written consent. The principal investigator will be responsible for monitoring the safety of the proposed experiments. Dr. McGloon and Jenkins will also execute the Data Safety Management (DSM) plan and provide any necessary progress reports to the IRB, including but not limited to subject demographics, recruitment rates, retention rates, quality assurance issues, and adverse events or significant adverse events. Dr. Jenkins or her designee, should she be unavailable, will be responsible for reporting all unanticipated problems or AEs to the IRB. The PI or Co-I will be present for patient visits and the OT Research Assistant will discuss any perceived AE with them. Dr. McGloon will be responsible for reporting any unanticipated device- related AE's to FDA. All screening data will be kept in a binder in Dr. McGloon's locked office. Screening data collected from participants who do not qualify for the study will be securely destroyed.

Dr. Mark George, who is a board-certified neurologist and psychiatrist, and Phillip Summers will oversee the use of the taVNS system. Dr. Jenkins will be immediately available to the RA to monitor safety and adverse events.

An independent Safety Monitoring Committee (SMC) will be formed to advise the study investigators. The SMC will review and evaluate accumulated study data to ensure safety, as in the pilot trial. They also will make recommendations concerning continuation, modification, or termination of any of the taVNS studies. It will be composed of Dr. Steve Kautz PT PhD and NM4R PI, Dr. Michelle Woodbury, OT PhD; and Dr. Jeff Borckardt, MUSC associate professor psychiatry and assistant provost with extensive VNS, TMS, and tDCS experience. The SMC and IRB will be notified immediately of any and all SAE's.

Drs. Jenkins, McGloon and Coker-Bolt will obtain informed consent for mother and infant to participate, during which participants' guardians are fully advised on the research procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse their infant's participation in the study without prejudice, their right to terminate participation of their infant at any moment without prejudice, and the name and telephone number of the principal investigator.

Regarding confidentiality, subjects' guardians are informed that the information they provide, as well as participation in the study, will be kept strictly confidential, with access limited to the research staff. All paper records (consents, CRFs, study tools) will be kept in Dr. McGloons' locked office in the College of Health Professions The identity of subjects in databases will be protected with alphanumeric codes. All data will be kept in locked office or on secure servers designed for use and access by Brain Stimulation and Neonatology, and OT Lab members only.

14.0 Withdrawal of Subjects

Parents may withdraw their infants at any time. Reasons may include excessive demands of time for CIMT or family pressures. Infants may be withdrawn without parental consent, if taVNS is poorly tolerated. If either occur, parents will be referred for clinical CIMT, of if this is not possible within the parent's home structure, other occupational and physical therapy as appropriate. We will continue to collect follow-up data on motor skills even with early termination, if infants continue with MUSC OT department.

15.0 Risks to Subjects

Risks of taVNS

taVNS is transcutaneous electrical stimulation of the auricular branch of the vagus nerve that innervates the ear. Although this novel therapeutic modality is still in the development and optimization process, few risks are expected by the peripheral taVNS in adults and infants. TENS devices are FDA approved for pain relief and are available over the counter. The main risks associated with TENS are electrical hazards that may result in user discomfort or injury. The unit used in these studies (Soterix) is a custom modified, FDA-cleared electrical stimulator that meets the standards of the FDA for investigational use. Skin irritation, redness, or inflammation may occur under the stimulating electrodes, but these have not been observed with short term use.

Two studies have used TENS on neonates to try to prevent or mitigate painful procedures (39-40). The TENS was administered at acupuncture sites with increasing current from 1-3.5 mA, and Hz from 2-10 in 30 healthy infants <3 days old. (39) In a subsequent study, this investigative team randomized 162 term neonates to TENS (3.5mA, 10Hz) or usual care to prevent pain from lancet heelsticks for blood sampling (40). These TENS parameters were safe and did not cause discomfort in the neonates. TENs has also been used with passive stretching in neonatal torticollis at 8Hz, 0.2mA for 30 minutes continuously (41) and in brachial plexus nerve injuries starting at 6 weeks of age to improve motor function of the hand, in conjunction with constraint induced movement therapy (42). Neither study reported adverse effects of electrical stimulation. TENS has also been used in peroneal and sacral nerve stimulation for dysfunctional voiding and stooling (44- 45). Finally, the routine sweat test employed in newborns and infants to confirm the diagnosis of cystic fibrosis uses transcutaneous electrical stimulation to deliver pilocarpine via iontophoresis (43). From the product brochure of the Nanoduct™ Neonatal Sweat Analysis System (Discovery Diagnostics, Canada), the nominal current is 0.5 (± 0.02) mA to 5 mA for 2.5 minutes (± 0.2 sec).

taVNS also has associated risks that may arise from the direct brain effects stimulating the vagus nerve. The transient decrease in heart rate is a well described risks associated with neuromodulation of the parasympathetic nervous system that we have also observed in infants in the administration of noninvasive taVNS. The decrease in heart rate of 20±10bpm from a baseline HR of 160bpm occurs within 30 seconds of onset of stimulation and resolves in 60 seconds.

There have been multiple studies in which taVNS has been used on humans, none of them reporting significant adverse events. A simple PubMed search for "transcutaneous auricular vagus nerve stimulation" shows more than 100 peer-reviewed articles, most of which have been

published within the past 5 years. An extremely through review of all tVNS literature has been performed and no harm or adverse events have been observed and any side effects were resolved by decreasing current intensity. There also is currently a commercial tVNS device available for purchase on the European market (Cerbomed - Nemos device; www.cerbomed.com) that is marketed as a take- home treatment for epilepsy.

Not only does the current literature show a lack of harm done by tVNS, the side effects of implanted VNS of alteration of voice, coughing, pharyngitis, hoarseness, headache, and nausea, have not been reported with taVNS. Cardiac evaluations have been made on hundreds of VNS, and more recently taVNS patients, with no changes in cardiac function (Handforth et al, 1998; Sackeim et al, 2001b; Morris and Mueller, 1999) with long-term safety confirmed in recent large sample retrospective studies (Menascu et al, 2013; Ryvlin et al, 2014; Choi et al, 2013).

We performed taVNS paired with feeding in 35 infants in our pilot study without adverse effects and with potential benefit. A summary of potential risks in infants include the risk of skin irritation, discomfort, transiently decreased heart rate, and loss of confidentiality. Bradycardia: Our own safety studies designate a transient measurable change in heart rate (-20 to 10bpm), lasting <60 seconds, which is not clinically significant in infants with baseline HR of 140- 160bpm in our pilot study (Badran BW, 2020, Frontiers in Human Neuroscience).

Given the minimal risk of taVNS FDA approved/cleared devices, we anticipate that taVNS paired with CIMT will be a very safe procedure in infants. The potential risks will be clearly outlined in the informed consent document, as in our prior infant taVNS study. MUSC's IRB has previously determined our taVNS system to be minimal risk device. Nevertheless, there may be unknown risks with experimental procedures.

Risk of loss of confidentiality: We will assign study numbers to each participant, keep CRF and consent forms in locked offices. Database files with names and contact information will be password protected and stored on the MUSC Pediatric server. All other data files related to this study will be identified by participant number only, without link to standard identifiers. We will publish the aggregate data only.

This study will involve research on vulnerable subjects: mothers and their infants with perinatal brain injury, potentially as a result of maternal conditions during pregnancy.

16.0 Potential Benefits to Subjects or Others

The infants with perinatally acquired brain injury constitute a vulnerable populations, but the procedures in this protocol are all minimal risk procedures (CIMT, motor assessments). Other than the novelty of using taVNS in infants, taVNS also involves little risk: equivalent TENS units are widely available on the internet for home purchase and use in all ages.

The intervention of pairing taVNS and CIMT could offer considerable benefit to both families and infants. taVNS paired with CIMT training may enhance infant motor skills in infants who

have one-sided weakness, and enable the infants to achieve greater upper extremity function with less time commitment than the maximum CIMT protocols that are 2 to 3 times as long as our taVNS-paired CIMT protocol.

However, there may be no direct benefit to the participants.

17.0 Sharing of Results with Subjects

Results of all motor skills test will be shared with parents as soon as the scoring is completed.

18.0 Drugs or Devices

The Soterix device and electrodes, hand-held trigger will be stored in Dr Coker-Bolt's or McGloon's office when not in use, and in a locked cabinet when in daily use for a participant. Only authorized investigators will have access to this locked cabinet.

The Soterix units is a custom device based on an taVNS device that is FDA cleared for investigational use. (see Soterix letter)

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