PROTOCOL TITLE:

Combining taVNS with early CIMT to improve health outcomes of infants

PRINCIPAL INVESTIGATOR:

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NCT05101707

1.0 Objectives / Specific Aims

Preterm birth and complications in term births increase infant morbidity and mortality. Premature rupture of membranes, intrauterine or systemic infection, diabetes, fetal-maternal hemorrhage and abruption lead to fetal distress and preterm delivery or hypoxia ischemia at term birth. These conditions result in increased risk for intraventricular hemorrhage, global hypoxia-ischemia (HIE), arterial stoke, and neuroinflammation with white matter injury in newborns of all gestational ages (GA).[1-5] CNS injuries then may manifest as early developmental delays and motor weakness in the first 12 months, that presage hemiplegic cerebral palsy (CP)**.**

Early targeted therapy interventions for high-risk infants aim to improve neurological outcomes by taking advantage of critical windows for neuroplasticity.[4,5] Intensive interventions, such as constraint-induced movement therapy (CIMT), are designed to ameliorate early motor predecessors of CP in at-risk infants.[6-13] This intervention must be provided at a minimally effective dosage of 40 hours,[13] and 60-120 hours for optimal outcomes, and are typically provided in a condensed time period, over 4 to 6 weeks with intensive task-practice for 3-6 hours a day.[6-13] Delivering CIMT within the context a typical family day is a challenge.[11] Interventional strategies that reduce the time requirement while offering the same or better outcomes would benefit families and facilitate treatment delivery.

Few studies have used neuromodulation combined with intensive motor therapies, such as CIMT, to enhance neuroplasticity and improve functional outcomes in children. Transcranial direct current stimulation has been used safely in older children with CP during bimanual learning therapy.[14,15] Our group is the first to use non-invasive transcutaneous auricular vagus nerve stimulation (taVNS) paired with a motor task of bottle-feeding in infants with feeding failure. taVNS paired with motor feeding activity was safe and over 50% [16,17] infants determined to need a gastrostomy tube (G-tube) attained full oral feeds (mean time to full oral feeds 15 days with once daily, and 7.8 days with twice daily treatment). With our unique collaboration of experts in brain stimulation, pediatric translational clinical science and pediatric occupational therapy in this pilot project, we are one of the few groups able to rapidly translate this neuromodulatory modality in older infants with hemiplegia undergoing CIMT treatment.

We propose to expand the paradigm of pairing neuromodulation with motor training in at-risk infants by **exploring the safety, feasibility, and effectiveness of delivering taVNS concurrently with CIMT.** Our hypothesis is that combining taVNS with intensive CIMT may boost neuroplasticity, allowing for delivery of infant therapy at a minimally effective dosage (40h)[13] while improving infant outcomes.

Aim 1: To determine the feasibility and safety of taVNS in at-risk infants 6-18mo undergoing CIMT therapy in open label pilot trial. We will assess the therapist's ability to deliver high-quality CIMT while delivering taVNS stimulation by videotaping the sessions and scoring randomly selected weekly treatment (20% sessions) with a CIMT fidelity measure we and others have used in CIMT studies.[13] Scores must meet or exceed therapist goals to show that taVNS can be delivered by the therapist without detracting from the delivery of high quality CIMT.

We expect in 6-18month old infants with unilateral motor weakness that taVNS paired with intensive CIMT will be safe and well tolerated and can be delivered with good fidelity by CIMT therapists.

Aim 2: To generate pilot data measuring infant response to 40h CIMT + taVNS stimulation in: 1) upper extremity motor abilities, 2) gross motor skills, and 3) individual treatment goals.

We expect infant motor skills to improve with 40h CIMT+ taVNS, from before to the end of treatment, with maintenance of motor skill gains at 3months after completion of CIMT (n=5 complete the course of CIMT+taVNS).

This is the first application combining neuromodulation and the proven intervention of CIMT in infants. We need to show feasibility and generate pilot data in a small number of patients prior to submission of an NIH proposal on pairing taVNS and CIMT for rehabilitation of infant s with hemiplegia after perinatal brain injury (see Ramey Letter of Support). This application expands our success with our previous NM4R pilot grant, which culminated in a taVNS infant system designated as an FDA Breakthrough Device. We will use this device in a completely unexplored area of neuromodulation, that of taVNS paired with intensive CIMT rehabilitation in young infants. Our goal with this combination neuromodulatory strategy is to decrease the severity of clinical deficits in infants, to improve day-to-day living, ameliorate life-long motor deficits, and help both the child and their families.

2.0 Background

Perinatal CNS injuries include brain dysmaturity after preterm birth, global ischemic or arterial stroke, severe intracranial hemorrhage and hydrocephalus, and sequelae of neuroinflammation due to intrauterine infection, maternal diabetes or maternal immune activation.[1-5] Perinatal CNS injuries have life-long impact via significant disruption of the normal developmental trajectory of neural circuits.[1,4,5] Abnormal connections, along with decreased populations of myelinating cells and inter-neurons, result in less myelination, fewer brainstem-cortical connections, and reduced corpus callosal and corticospinal tract volume and connections.[1,3-5] Even with developmental plasticity,[5] there are frequently significant deficits following perinatal insult.

Many conditions that contribute to perinatal brain injury may not be reliably predicted. Further, evidence-based neuroprotective treatments are very limited and must be delivered shortly before or after delivery. **Therefore, novel rehabilitation approaches that improve infant morbidity are needed.**

Motor weakness is frequently the first manifestation in young infants of later significant motor impairments. Standard pediatric rehabilitation programs, such as CIMT, maximize the movement and functional abilities of motor-impaired children through the use of high-dose intensive and child-active rehabilitation strategies.[6-11,13] Multiple investigations of CIMT show clinically meaningful and sustained benefits with high levels of scientific evidence.[10-13] While CIMT protocols vary, the most efficacious protocols use dosage between 60-120 treatment hours,[9,13] within a condensed time period, frequently multi-hour sessions daily for 4weeks. There is substantial evidence that such intensive therapeutic bursts (e.g., many hours each day on multiple consecutive days across multiple weeks) create opportunities for the development of increased motor and functional skills in infants with early motor delays. Thus, activity-dependent neuroplasticity is reinforced through intense repetition.[12] However, these early intensive therapy models are difficult to accomplish in many households.[11]

There is evidence 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, near-normal outcomes.[17-24] Adjunctive neuromodulation that increases the efficiency of CIMT, might lessen the burden on infants, therapists and parents. Therefore, our premise is that in babies with unilateral motor weakness after perinatal brain injury, brain stimulation via taVNS simultaneously delivered with CIMT will boost motor cortical plasticity involved in motor tasks, with better function in a shorter time.

The data in animals and humans support the premise that both cervically-implanted and transcutaneous auricular VNS 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] In adult stroke patients, upper extremity Fugl–Meyer scores significant increase with VNS-paired rehabilitation vs rehabilitation alone.[25,-27] An FDA pivotal study of cervical-VNS for adult stroke (NCT03131960) [31] is reporting clinically and statistically significant functional improvement

with active vs sham VNS paired with rehabilitation. Similar results are being obtained with non-invasive VNS by stimulating the auricular branch of the vagus nerve located in the ear with a transcutaneous electrical nerve stimulation (TENS) device.[16,17, 30-32] An ongoing MUSC COBRE trial is also using taVNS-paired with upper limb rehabilitation in adult stroke patients (Badran, PI; NCT 04129242). In infants, TENS devices are FDA-approved for pain management. TENS serves as the basis for the Soterix Medical taVNS unit used in our infant feeding trial and this proposed study. We have conducted safety and feasibility trials of taVNS in infants with oromotor disability due to perinatal brain injury and observed no minor or major adverse effects.[16,17] Our work validates parameters for delivering taVNS, suggesting that two-minute taVNS periods at 500μs, 25Hz, and slightly less than perceptual threshold (PT) are safe, tolerable and produce changes in white matter microstructure consistent with neuroplasticity in infants.[16,17, 33-35] (see preliminary data)

Activation of afferent vagal fibers in the dorsal nucleus and locus coeruleus along with an associated stimulus, results in secretion of norepinephrine, a high-alert signal that helps activate motor to hippocampal pathways and re-establish normal connections. Dr. Badran has shown via fMRI that taVNS also activates key sensorimotor targets in adults, including thalami and basal ganglia that are also key areas of perinatally acquired CNS injury.[33] We also changes in white matter microstructure consistent with neuroplasticity in infants following taVNS-paired feeding (preliminary data). Thus, a non-invasive taVNS approach may be particularly effective in infants who manifest early motor disabilities due to perinatal brain injury and whose developmental and reparative plasticity is greater than for adults.[5]

We envision that CIMT paired with taVNS may boost neuroplasticity and allow for delivery of intensive therapy at a **minimal dosage of 40h** while improving infant outcomes. Ultimately CIMT pairing with taVNS may be used in the hospital, clinic or home setting to improve motor dysfunction, reduce the incidence or severity of hemiplegic CP, and decrease financial and emotional costs of caring for a child with motor disability. This would significantly improve the quality of life for these children with disabilities. *Importantly, this noninvasive technology may be effective in rehabilitation, even when other neuroprotective treatments are not available, as many conditions leading to motor disorders in infants are unpredictable or unavoidable*. Significance of this pilot proposal is enhanced by the following:

- We will generate pilot data on feasibility and gather data on effect for taVNS in infants getting standard of care CIMT for rehabilitation after perinatally acquired brain injury and stroke.
- A collaborative, innovative multidisciplinary team will execute these proposed studies, including Dr. Coker-Bolt an expert in infant CIMT and taVNS expert (Badran).
- The infant taVNS system for this study allows the therapist to control the delivery of taVNS with the intent of ultimately developing home-based CIMT therapies.

INNOVATION

Application of neuromodulation to perinatally acquired brain injury is innovative. Activity-dependent plasticity that is enhanced by electrical stimulation is just beginning to be translated to infants after perinatal brain injury.[16,17] CIMT plus transcranial direct current stimulation is being tested by Dr Gillick's group in older children and adults with cerebral palsy.[14,15] VNS was pioneered by Dr. George, and non-invasive transcutaneous auricular VNS (taVNS) was developed by Drs. Badran and George. With the collaboration of brain stimulation experts, occupational therapists, neuroradiologists, and a neonatal clinical translational investigator, **we are the first to use taVNS in infants and neonates**.[16,17] In our infants with brain dysmaturity or overt brain injury, we postulated that neuromodulation with non-invasive taVNS may positively influence abnormal circuits to improve neuronal connectivity and neuroplasticity and improve oromotor skills. Importantly, taVNS was well accepted by parents and care providers.

Infant CIMT have been shown to have a positive influence on early motor abilities and hand function,[13,36-39] but current models continue to require 60-120 hours of intensive therapy, including the recently funded Intensive Infant Rehabilitation (I-ACQUIRE, NCT03910075) Phase III Clinical Trial. These intensive therapy models raise challenges for parents juggling the family's daily schedule.[11] Using two innovative and potentially effective therapies in young infants, we aim to decrease the time commitment and improve outcomes.

Overview of Innovation: This proposal will use the following innovative techniques and goals

- A novel, portable, therapist-triggered taVNS system that can be used during CIMT sessions
- A novel cohort of older infants with unilateral weakness who are referred to CIMT therapy
- Safety and feasibility of taVNS paired with CIMT
- Assessment of therapist delivering CIMT with high fidelity using a CIMT fidelity tool [13]

To our knowledge, no other investigators are treating young infants who have perinatally acquired brain injury with CIMT+ taVNS to improve motor skills or developing a similar treatment paradigm.

Preliminary data from pilot trial of taVNS in infant feeding

We have significant experience with taVNS for feeding failure in infants from our pilot trial of taVNS-paired feeding, who were refractory to standard of care early feeding interventions and were slated to receive a G-tube. We obtained IRB approval with medical device designation of non-significant risk for this open- label trial with parental consent.

Inclusion Criteria of previous taVNS feeding trial: Infants born ≤ 33 completed weeks gestation, or with brain injury (HIE); clinically stable; failing oral feeding; clinical team discussing need for G-tube with parents.

Exclusion Criteria of taVNS feeding trial: Cardiomyopathy, significant respiratory support

Primary Efficacy Outcomes: Increase in total daily oral feeding volumes compared before and during treatment, achievement of full oral feeds (≥130ml/kg/d with weight gain), avoiding G-tube.

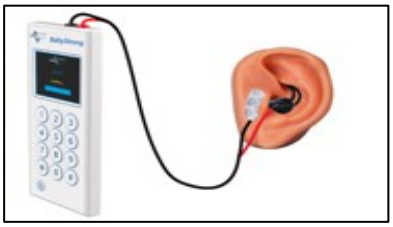
Secondary Efficacy outcomes: Brain changes measured by diffusion imaging (DKI) in white matter tract (WM) integrity before and after taVNS-paired feeding, normalized for weeks of development. Improvement in overall motor function by Specific Test of Early infant Motor Performance (STEP).[40]

Primary Safety Outcomes: Bradycardia (HR<80bpm for 5 seconds), as potential effect of taVNS on the dorsal nucleus and efferent cardiac vagus nerve fibers; skin irritation; Change >3 points in the Neonatal and Infant Pain scale (NIPS).[41,42]

Treatment Protocol:

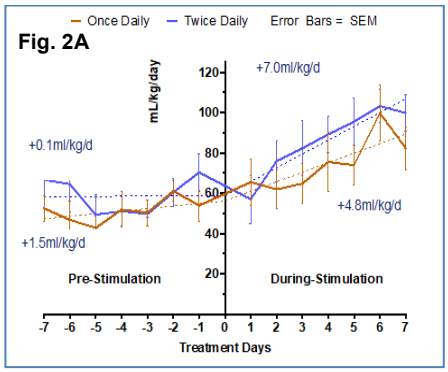
- taVNS pulses delivered via a left ear electrode at 25Hz, pulse width 500μseconds**.**
- Perceptual threshold (PT) determined by increasing current slowly until infant detects tingling with facial change or shrug.
- taVNS delivered at 0.1mA < PT, paired with suck-swallowing during one (n=15) or two (n=18) oral feedings per day, for 2-4 wks.

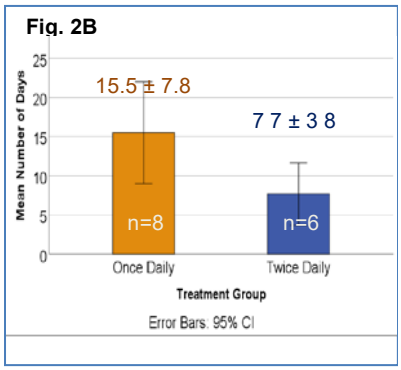
Fig. 1. Operator-controlled taVNS system: Baby bottle sleeve has a button trigger and wired connection to Soterix taVNS unit, with wired electrode on left tragus, as shown. We deliver taVNS by manual trigger coordinated with visible suck-swallow.



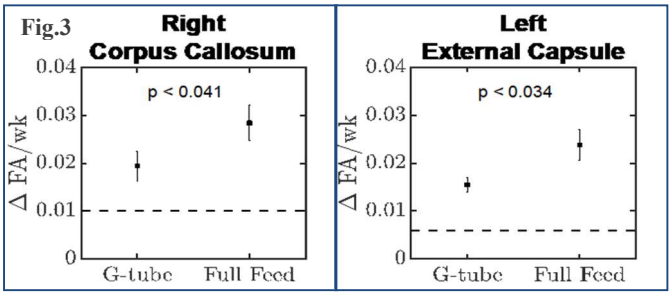
Results:

Efficacy outcomes: To date, 19/35 infants destined for G-tube attained full oral feeds with taVNS paired feedings (54% Responders). taVNS Responders showed a significant increase in mean daily po volumes vs Non-Responders who received G-tube ($p<0.05$). We also demonstrate a dose response with greater increase in slopes of daily po feeding volumes (F, 8.05, p=0.01, **Fig. 2A**) and shorter time to full po feeds ($p<0.05$, **Fig. 2B**) in twice vs once daily treatments.

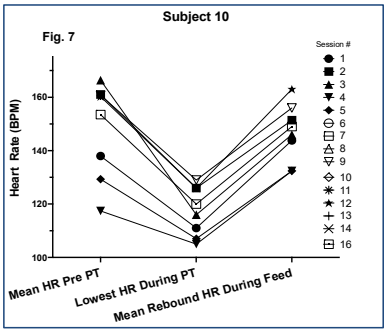


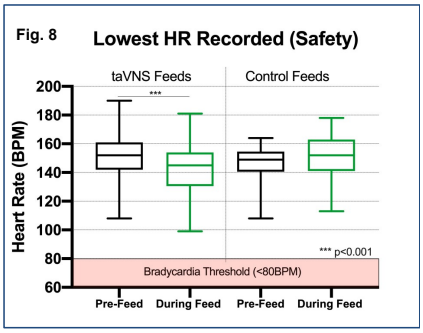


Secondary efficacy outcomes: dMRI before and after taVNS treatment, shows white matter plasticity changes in fractional anisotropy (FA) that are significantly greater for Responders versus Non-Responders in corpus callosum and external capsule, per week of development (**Fig. 3**). Both groups showed greater than normal FA increase, compared with published normal developmental changes (indicated by dashed line).[43]



Target attainment: Transient HR decrease was reliably demonstrated within 30sec of taVNS onset, with a quick rebound in 60sec. The HR decrease was reproducible within and across individuals. **Fig. 4** shows the consistency of heart rate changes before, at onset of taVNS, and during 1st 5 min of feed over all sessions for one subject. **Fig. 5** shows significantly lower HR during onset of taVNS-paired feeds compared with pre-feed, and no HR change during control feeds without stimulation.





Safety outcomes: We observed no bradycardia (HR<80bpm 5sec) & no skin irritation. Persistent increase in discomfort scores NIPS >3 occurred in 3 of 228 sessions (1.3%) and resolved 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.[16,17]

Other Achievements that impact this proposal: We recently received Breakthrough Device designation from the FDA for the BabyStrong device, which is similar to the system proposed in this application. Our phase I STTR early RCT with the BabyStrong system (Jenkins, Badran, MUSC FRD Accel), received a favorable score from NICHD STTR study section with notification of probable funding after council review.

Our infant taVNS feeding data,[16-17] our early FDA breakthrough device development for young infants, and other studies indicating positive results of taVNS paired with motor learning in adults,[26-32] support study of this neuromodulatory technique in infants with significant motor deficits of hemiplegia after perinatally

acquired brain injury.

3.0 Intervention to be studied

Proposed Trial of CIMT Paired with taVNS

We will treat up to 10 infants referred for CIMT with one-sided motor weakness to receive active taVNS paired with 40 hours of CIMT. We will perform infant motor assessments before and after the treatment is completed to answer the following questions:

1) Is taVNS feasible and safe of in infants 6-18months of age undergoing CIMT therapy?
2) Does infant motor ability increase with low-dosage 40h CIMT + active taVNS as measured by: 1) upper extremity motor abilities, 2) gross motor skills, and 3) individual treatment goals.

Experimental set-up: For this proposal we will modify our BabyStrong system, which uses the FDA cleared Soterix taVNS unit, Neolead® electrode in front of the tragus and custom ear electrode for infant sized ears, wired trigger control of stimulation with a trigger button or direct input in the Soterix taVNS unit. We will substitute a portable, therapist-triggered taVNS system with hand held trigger button as seen in **Figure 6**. The therapist will activate a hand-held button for 2min-on/30 sec-off control of stimulation during a CIMT session.

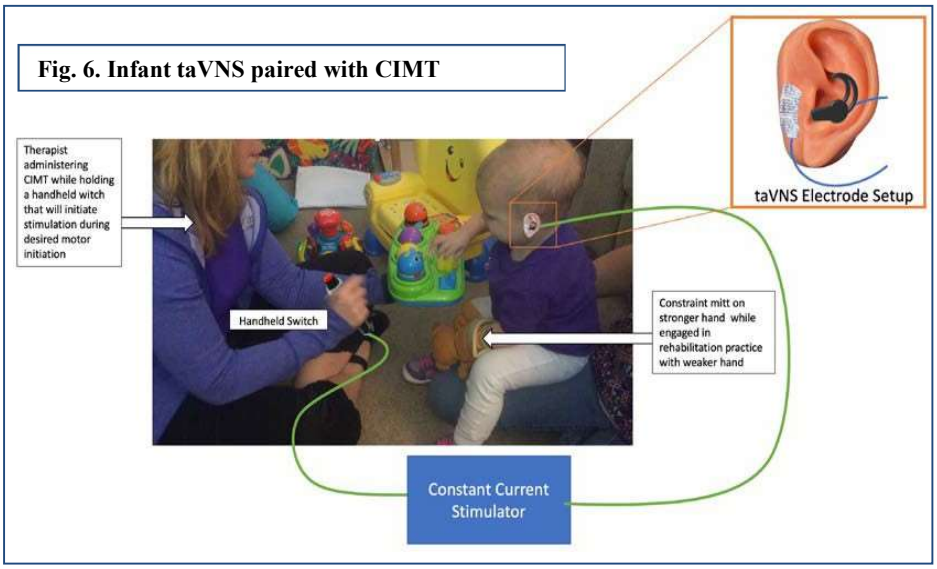


Fig. 6. Infant taVNS paired with CIMT

We have an established, collaborative, innovative multidisciplinary team to execute these proposed studies. In addition to MUSC's infant taVNS trial, Drs. Jenkins and Coker-Bolt have been collaborating for 10 years on infant developmental assessments and other therapeutic studies. Dr. Coker-Bolt has been an innovator in CIMT in young infants and has investigated modified CIMT approaches in the U.S. and abroad.[37,45-47] These studies provided evidence of how to modify signature pediatric CIMT approaches, while adhering to the essential elements of the therapy, to assure high levels of treatment efficacy. Pertinent to this trial, she also published the first case report on successful implementation of CIMT in infants under one year of age.[37]

Working with development, perhaps activating critical motor synapses, taVNS paired with CIMT could deliver groundbreaking innovation in the increasing problem of unilateral motor weakness in infants with perinatally acquired brain injury.

Aim 1. To determine the feasibility and safety of taVNS in 6-18mo infants with unilateral motor weakness undergoing CIMT therapy in an open label pilot trial. The CIMT therapy sessions will be videotaped and a random weekly session (20% sessions) will be scored for CIMT treatment fidelity while the therapist is delivering taVNS. Dr. Coker-Bolt will score these using a CIMT fidelity scoring system previously used in other studies.[13] Scores that meet or exceed therapist goals indicate that taVNS can be delivered by the therapist while delivering high quality CIMT.

Aim 1 Procedures:

1) We will follow the following protocol for CIMT paired with taVNS with one OT therapist delivering CIMT with a brain stimulation research assistant (BSL-RA) supervising the delivery of taVNS:
2) Hydrogel electrodes are placed in front of tragus, and inner tragus/cymba chonchae, securing the wires behind head with tape, and placing wire under shirt.
3) CIMT and BSL therapists will establish perceptual threshold (PT) daily, increasing +0.1mA, until infant shows signs of tingling sensation.
4) We will treat with stimulation at 0.1mA<PT, 500µsec, 25Hz, during each CIMT session.
5) The OT therapist delivering CIMT will start stimulation by pushing the button for a continuous 2min-on, 30sec-off program (similar to taVNS-feeding settings[16,17]), while administering CIMT. Trigger button is off for rest.
6) Impedance is constantly displayed on the Soterix unit (*good*, *moderate* or *poor*). If contact is *poor,* a beep alerts the therapist and the BSL RA will adjust the electrode to ensure contact and delivery of stimulation.
7) Both parent and OT will be queried by weekly questionnaire to assess their perception of ease of use, infant tolerance, general acceptance and any recommendations for improvement of taVNS delivery during the 4 weeks of CIMT therapy.

Table 1. Key Features of Routine Infant CIMT Program	
Dosage	Each session will be 2 hours, 5 sessions each week, over 4 consecutive weeks for a total dosage of 40 hours.
Therapy setting	MUSC's pediatric OT lab, fully equipped with mats, benches, toys for pediatric rehabilitation equipment
Type of constraint	We fabricate custom-made hand splint/orthotics for the infant's less-affected hand and place a soft mitt on this splint, as we have used in prior CIMT trials. The constraint mitt will only be worn during the therapy sessions. [36-39]
Therapist	Highly trained therapists trained in the principles of pediatric CIMT[38] will use immediate and varied reinforcement, primarily verbal praise, smiles, and supportive gestures, to sustain the infant's attention, engagement, and enjoyment, then "shape" a movement by using prompts and increasing the demands for greater precision, strength, fluency (coordination), and speed, using technique of "successive approximations". The therapist implements a "MR3 cycle," of Movement, Reinforcement, Repetition, and Refinement, used in the I-ACQUIRE Phase II clinical trial to progress the child in increments as skills increase
Components of infant CIMT	Sessions will actively engage the infant to initiate, attempt, repeat, practice, and refine a wide range of age developmentally appropriate skills and movements using the more-impaired arm and hand. Emphasis will be on engagement of the infant and the affected upper extremity in age- appropriate activities in positions of supine,

sessions	prone, sitting, quadruped, and supported standing.
Documentation for each session	Therapist will keep formal daily therapy logs and ask mothers to report on activities and progress at each session. Therapist and mothers will jointly review targeted therapy goals at each session.
Discharge program	Therapist and parents develop a practical written plan to maintain gains made during the CIMT program. The plan will involve motor skills and functional activities appropriate for the infant's age at discharge from the program.

Technical administration of taVNS: The therapist will need assistance with learning the taVNS trigger system and integrating it with CIMT. 1) We will provide training sessions for the single designated CIMT therapist who will perform all interventions before enrolling patients, and 2) the BSL RA will supervise and assist with taVNS treatments with each patient session. The brain stimulation RA will be trained to deliver stimulation, place the ear electrode for good impedance readings, and demonstrate this with Dr. Jenkins or Badran prior to supervising the CIMT therapist. We have several RAs who are experienced in infant taVNS who may also supervise any new RAs in the procedures. As part of this training, we have an instructional video for setting up the taVNS system with an infant.

Limitations and alternative approaches: The therapist may provide feedback that a different trigger switch is needed or a different program with a '2min on-30sec-off' loop that does not require pressing the button repeatedly. We will then incorporate this feedback in our next design of the trigger. Previous NIH reviewers of our similar Soterix-based BabyStrong STTR phase I were concerned about overstimulation, requesting a fail-safe stop time for each trigger. We are using the same infant-modified Soterix taVNS unit, and for establishing safety in this CIMT+taVNS pilot we will use the same duty cycle of 2min-on, 30sec-off. For safety the taVNS unit limits deliverable microcurrent is limited to a maximum of 2mA, which is sufficient for adults to register a tingling. Feasibility of using wired ear electrodes: The infant should be engaged during CIMT such that the ear electrode does not irritate the infant. If the first infant does not tolerate the ear electrode, we will train infants on the electrode by having the mother place the electrode on the ear prior to the session and at home, to get the infant used to ignoring the presence of the electrode. The electrode should not impact hearing during the session. In our pilot trial infants received a hearing screen before discharge, all infants passed the screen except one, and that infant failed the hearing screen before taVNS treatment was initiated. No hearing adverse events were noted in that pilot trial.

Feasibility of delivering high fidelity CIMT with taVNS: We expect the therapist to maintain high fidelity of CIMT delivery while delivering taVNS over the weeks of treatment for the first infant. If the BSL RA has to assist in most therapy sessions after week 1, we will troubleshoot any sticking points and retrain the therapist so that the CIMT flow is minimally interrupted by triggering taVNS. If the therapist is not able to achieve high fidelity scores of 3 on all items by week 2 of treating the first infant, we will have the BSL RA assist with all sessions to ensure CIMT delivery, and if funds exist, incorporate design changes to increase therapist efficiency with the taVNS system during CIMT.

Aim 2: To measure infant response to low-dosage 40h CIMT + active taVNS stimulation (n=5) in: 1) upper extremity motor abilities, 2) gross motor skills, 3) individual treatment goals before and at the end of CIMT treatment. We will assess motor skills at 3mo after completion of CIMT for maintenance of gains.

4.0 Study Endpoints

Aim 1: Primary CIMT feasibility outcomes: Ability of therapist to operate taVNS easily and successfully by earning a meeting or exceeding score (3 or 4) on random videotaped therapy sessions, as scored by CIMT fidelity treatment.

Aim 1: Primary taVNS safety and feasibility outcomes: Ability of infant to tolerate wired ear electrode and for electrode to remain securely in place with good contact with minor manipulation during sessions; <5% of sessions with sustained discomfort requiring decreasing current.

Aim 2: Primary Efficacy Outcome: We will use the Quality of Upper Extremity Skills Test (QUEST) subtests for grasp and dissociated movement as our primary outcome. The QUEST is a reliable, valid, quantitative outcome measure with excellent psychometric properties, and is recommended by NINDS/NICHD for the evaluation of movement patterns and hand function in children with cerebral palsy.[49] The subtests for grasp and dissociated movement have been used in published infant CIMT trials,[8] and provide detailed information on hand function and quality of movement between the right and left sides of the body.

Aim 2: Secondary Efficacy Outcomes: We will use three other assessments for fine and gross motor function and meeting individual treatment goals: Developmental Assessment of Young Children (DAYC), the Gross Motor Function Measure-66 (GMFM-66) and the Goal Attainment Scale (GAS).

- The DAYC is a standardized assessment of early developmental skills from birth to 5 years of age[50] and is recommended for early detection of CP.[51] We will use the DAYC Physical Development domain to assess developmentally appropriate fine and gross motor skills. [Mean (SD)=100±15 for each domain.]
- We will use the GMFM-66 as a comprehensive evaluation of foundational gross motor skills to assess how much of a task the infant can do rather than the quality of motor performance.[48,52,53] Specific sections tested include Dimensions (A) Lying & rolling, (B) Sitting, (C) Crawling & kneeling, (D) Standing. [52,53]
- The GAS is an individualized outcome measure that is standardized in order to calculate the extent to which a patient or group of patients' therapy goals are met.[54,55] We will set individual goals for each infant and use the GAS scale to analyze differences between before and after CIMT+taVNS.

5.0 Inclusion and Exclusion Criteria/ Study Population

- **Inclusion Criteria:** Infants, 6-18 months old with hemiplegia/motor asymmetry who qualify for CIMT, Gross Motor Function Classification System (GMFCS) level I-IV (a validated classification system with 5-levels that describe the gross motor function of children with cerebral palsy based on their self-initiated movements, in sitting, walking and mobility).[48] Prior CIMT therapy will be allowed if the infant has not had CIMT in the preceding 3 months.
- **Exclusion Criteria:** GMFCS level V,[48] severe motor impairment/quadriplegic involvement; uncorrected blindness or deafness, cardiomyopathy. CIMT therapy within the prior 3 months.

6.0 Number of Subjects

We will enroll up to 10 infants aiming to collect data on at least 5 completed courses of CIMT+taVNS.

7.0 Setting

CIMT treatment sessions will occur in College of Health Professions (CHP) pediatric therapy lab located in the CHP B Building at 151 Rutledge Ave.

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. 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.

10.0 Study Design / Methods

Overall Study Design: This study will determine the feasibility, and safety of therapist-directed taVNS paired with CIMT therapy in n=10, 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.

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 5-10 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

The participants who receive active taVNS involved with this proposal will be infants whose participation is agreed to by their guardians in written consent, and their mothers. The principal investigator will be responsible for monitoring the safety of the proposed experiments. Dr. 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. Badran will be responsible for reporting any unanticipated device- related AE's to FDA. All screening data will be kept in a binder in Dr. Jenkins' 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 Dr. Badran 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. 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.

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. 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.

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 Lab members only. 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.

Videotapes will be stored for future use, by Dr. 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 our research.

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 USC 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)

REFERENCES

[1] Duerden EG, Foong J, Chau V, Branson H, Poskitt KJ, Grunau RE, et al. Tract-Based Spatial Statistics in Preterm-Born Neonates Predicts Cognitive and Motor Outcomes at 18 Months. AJNR Am J Neuroradiol. 2015;36:1565-71.

[2] Bastek JA, Gomez LM, Elovitz MA. The role of inflammation and infection in preterm birth. Clin Perinatol. 2011;38:385-406.

[3] O'Shea TM, Joseph RM, Kuban KC, Allred EN, Ware J, Coster T, et al. Elevated blood levels of inflammation-related proteins are associated with an attention problem at age 24 mo in extremely preterm infants. Pediatr Res. 2014;75:781-7.

[4] Yanni D, Korzeniewski SJ, Allred EN, Fichorova RN, O'Shea TM, Kuban K, et al. Both antenatal and postnatal inflammation contribute information about the risk of brain damage in extremely preterm newborns. Pediatr Res. 2017;82:691-6.

[5] Dammann O, Leviton A. Inflammation, brain damage and visual dysfunction in preterm infants. Semin Fetal Neonatal Med. 2006;11:363-8.

[6] Glombik K, Trojan E, Kurek A, Budziszewska B, Basta-Kaim A. Inflammatory Consequences of Maternal Diabetes on the Offspring Brain: a Hippocampal Organotypic Culture Study. Neurotox Res. 2019;36:357-75.

[7] Nelson SM, Sattar N, Freeman DJ, Walker JD, Lindsay RS. Inflammation and endothelial activation is evident at birth in offspring of mothers with type 1 diabetes. Diabetes. 2007;56:2697-704.

[8] Rocha-Ferreira E, Hristova M. Plasticity in the Neonatal Brain following Hypoxic-Ischaemic Injury. Neural Plast. 2016;2016:4901014.

[9] Kwon JY, Chang WH, Chang HJ, Yi SH, Kim MY, Kim EH, et al. Changes in diffusion tensor tractographic findings associated with constraint-induced movement therapy in young children with cerebral palsy. Clin Neurophysiol. 2014;125:2397-403.
[10] Case-Smith J, DeLuca SC, Stevenson R, Ramey SL. Multicenter randomized controlled trial of pediatric constraint-induced movement therapy: 6-month follow-up. Am J Occup Ther. 2012;66:15-23.
[11] Case-Smith J, Frolek Clark GJ, Schlabach TL. Systematic review of interventions used in occupational therapy to promote motor performance for children ages birth-5 years. Am J Occup Ther. 2013;67:413-24.
[12] DeLuca SC, Trucks MR, Wallace DA, Ramey SL. Practice-based evidence from a clinical cohort that received pediatric constraint- induced movement therapy. J Pediatr Rehabil Med. 2017;10:37-46.
[13] Bella GP, Garcia MC, Spadari-Bratfisch RC. Salivary cortisol, stress, and health in primary caregivers (mothers) of children with cerebral palsy. Psychoneuroendocrinology. 2011;36:834-42.
[14] Raina P, O'Donnell M, Rosenbaum P, Brehaut J, Walter SD, Russell D, et al. The health and well-being of caregivers of children with cerebral palsy. Pediatrics. 2005;115:e626-36.
[15] Porter BA, Khodaparast N, Fayyaz T, Cheung RJ, Ahmed SS, Vrana WA, et al. Repeatedly pairing vagus nerve stimulation with a movement reorganizes primary motor cortex. Cereb Cortex. 2012;22:2365-74.
[16] Dawson J, Pierce D, Dixit A, Kimberley TJ, Robertson M, Tarver B, et al. Safety, Feasibility, and Efficacy of Vagus Nerve Stimulation Paired With Upper-Limb Rehabilitation After Ischemic Stroke. Stroke. 2016;47:143- 50.
[17] Khodaparast N, Kilgard MP, Casavant R, Ruiz A, Qureshi I, Ganzer PD, et al. Vagus Nerve Stimulation During Rehabilitative Training Improves Forelimb Recovery After Chronic Ischemic Stroke in Rats. Neurorehabil Neural Repair. 2016;30:676-84.
[18] Hays SA, Khodaparast N, Hulsey DR, Ruiz A, Sloan AM, Rennaker RL, 2nd, et al. Vagus nerve stimulation during rehabilitative training improves functional recovery after intracerebral hemorrhage. Stroke. 2014;45:3097-100.
[19] Khodaparast N, Hays SA, Sloan AM, Fayyaz T, Hulsey DR, Rennaker RL, 2nd, et al. Vagus nerve stimulation delivered during motor rehabilitation improves recovery in a rat model of stroke. Neurorehabil Neural Repair. 2014;28:698-706.
[20] Khodaparast N, Hays SA, Sloan AM, Hulsey DR, Ruiz A, Pantoja M, et al. Vagus nerve stimulation during rehabilitative training improves forelimb strength following ischemic stroke. Neurobiol Dis. 2013;60:80-8.
[21] Capone F, Miccinilli S, Pellegrino G, Zollo L, Simonetti D, Bressi F, et al. Transcutaneous Vagus Nerve Stimulation Combined with Robotic Rehabilitation Improves Upper Limb Function after Stroke. Neural Plast. 2017;2017:7876507.
[22] Meyers EC, Solorzano BR, James J, Ganzer PD, Lai ES, Rennaker RL, 2nd, et al. Vagus Nerve Stimulation Enhances Stable Plasticity and Generalization of Stroke Recovery. Stroke. 2018.
[23] Kilgard MP. Harnessing plasticity to understand learning and treat disease. Trends in neurosciences. 2012;35:715-22.
[24] Badran BW, Jenkins DD, Cook D, Thompson S, Dancy M, DeVries WH, et al. Transcutaneous Auricular Vagus Nerve Stimulation-Paired Rehabilitation for Oromotor Feeding Problems in Newborns: An Open-Label Pilot Study. Frontiers in Human Neuroscience. 2020.
[25] Badran BW, Jenkins DD, DeVries WH, Dancy M, Summers PM, Mappin GM, et al. Transcutaneous auricular vagus nerve stimulation (taVNS) for improving oromotor function in newborns. Brain Stimul. 2018;11:1198-200.
[26] Steenbergen L, Sellaro R, Stock AK, Verkuil B, Beste C, Colzato LS. Transcutaneous vagus nerve stimulation (tVNS) enhances response selection during action cascading processes. Eur Neuropsychopharmacol. 2015;25:773-8.
[27] Ventureyra EC. Transcutaneous vagus nerve stimulation for partial onset seizure therapy. Child's Nervous System. 2000;16:101-2.

[28] Redgrave JN, Moore L, Oyekunle T, Ebrahim M, Falidas K, Snowdon N, et al. Transcutaneous Auricular Vagus Nerve Stimulation with Concurrent Upper Limb Repetitive Task Practice for Poststroke Motor Recovery: A Pilot Study. J Stroke Cerebrovasc Dis. 2018.
[29] Badran BW, Dowdle LT, Mithoefer OJ, LaBate NT, Coatsworth J, Brown JC, et al. Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: A concurrent taVNS/fMRI study and review. Brain Stimul. 2018;11:492-500.
[30] Badran BW, Mithoefer OJ, Summer CE, LaBate NT, Glusman CE, Badran AW, et al. Short trains of transcutaneous auricular vagus nerve stimulation (taVNS) have parameter-specific effects on heart rate. Brain Stimul. 2018.
[31] Badran BW, Jenkins DD, Cook D, Thompson S, Dancy M, DeVries WH, et al. Transcutaneous Auricular Vagus Nerve Stimulation-Paired Rehabilitation for Oromotor Feeding Problems in Newborns: An Open-Label Pilot Study. Frontiers in Human Neuroscience. 2020;14.
[32] Badran BW, Yu AB, Adair D, Mappin G, DeVries WH, Jenkins DD, et al. Laboratory Administration of Transcutaneous Auricular Vagus Nerve Stimulation (taVNS): Technique, Targeting, and Considerations. J Vis Exp. 2019.
[33] Fang J, Egorova N, Rong P, Liu J, Hong Y, Fan Y, et al. Early cortical biomarkers of longitudinal transcutaneous vagus nerve stimulation treatment success in depression. Neuroimage Clin. 2017;14:105-11.
[34] Gillick B, Rich T, Nemanich S, Chen CY, Menk J, Mueller B, et al. Transcranial direct current stimulation and constraint-induced therapy in cerebral palsy: A randomized, blinded, sham-controlled clinical trial. Eur J Paediatr Neurol. 2018;22:358-68.
[35] Nemanich ST, Rich TL, Chen CY, Menk J, Rudser K, Chen M, et al. Influence of Combined Transcranial Direct Current Stimulation and Motor Training on Corticospinal Excitability in Children With Unilateral Cerebral Palsy. Front Hum Neurosci. 2019;13:137.
[36] De Ridder D, Vanneste S, Engineer ND, Kilgard MP. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. Neuromodulation. 2014;17:170-9.
[37] Kilgard MP. Harnessing plasticity to understand learning and treat disease. Trends Neurosci. 2012;35:715-22.
[38] Lowes LP, Mayhan M, Orr T, Batterson N, Tonneman JA, Meyer A, et al. Pilot study of the efficacy of constraint-induced movement therapy for infants and toddlers with cerebral palsy. Phys Occup Ther Pediatr. 2014;34:4-21.
[39] Coker P, Lebkicher C, Harris L, Snape J. The effects of constraint-induced movement therapy for a child less than one year of age. NeuroRehabilitation. 2009;24:199-208.
[40] Eliasson AC, Nordstrand L, Ek L, Lennartsson F, Sjostrand L, Tedroff K, et al. The effectiveness of Baby-CIMT in infants younger than 12 months with clinical signs of unilateral-cerebral palsy; an explorative study with randomized design. Res Dev Disabil. 2018;72:191-201.
[41] Gower L, Jenkins D, Fraser JL, Ramakrishnan V, Coker-Bolt P. Early developmental assessment with a short screening test, the STEP, predicts one-year outcomes. Journal of perinatology : official journal of the California Perinatal Association. 2018.
[42] Gallo AM. The fifth vital sign: implementation of the Neonatal Infant Pain Scale. J Obstet Gynecol Neonatal Nurs. 2003;32:199-206.
[43] Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Netw. 1993;12:59-66.
[44] Partridge SC, Mukherjee P, Henry RG, Miller SP, Berman JI, Jin H, et al. Diffusion tensor imaging: serial quantitation of white matter tract maturity in premature newborns. Neuroimage. 2004;22:1302-14.
[45] Miller SP, Vigneron DB, Henry RG, Bohland MA, Ceppi-Cozzio C, Hoffman C, et al. Serial quantitative diffusion tensor MRI of the premature brain: development in newborns with and without injury. J Magn Reson Imaging. 2002;16:621-32.
[46] Coker-Bolt P, DeLuca SC, Ramey SL. Training Paediatric Therapists to Deliver Constraint-Induced Movement Therapy (CIMT) in Sub-Saharan Africa. Occup Ther Int. 2015;22:141-51.

[47] Coker-Bolt P, Downey RJ, Connolly J, Hoover R, Shelton D, Seo NJ. Exploring the feasibility and use of accelerometers before, during, and after a camp-based CIMT program for children with cerebral palsy. J Pediatr Rehabil Med. 2017;10:27-36.
[48] Coker P, Karakostas T, Dodds C, Hsiang S. Gait characteristics of children with hemiplegic cerebral palsy before and after modified constraint-induced movement therapy. Disabil Rehabil. 2010;32:402-8.
[49] Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. Dev Med Child Neurol. 2008;50:744-50.
[50] DeMatteo C, Law M, Russell D, Pollock N, Rosenbaum P, Walter S. QUEST: Quality of Upper Extremity Skills Test. Hamilton, ON: McMaster University, CanChild Centre for Childhood Disability Research.; 1992.
[51] Swartzmiller M. Test Review: Developmental Assessment of Young Children–Second Edition (DAYC-2). Journal of Psychoeducational Assessment. 2014;32:577-80.
[52] Spittle AJ, Morgan C, Olsen JE, Novak I, Cheong JLY. Early Diagnosis and Treatment of Cerebral Palsy in Children with a History of Preterm Birth. Clin Perinatol. 2018;45:409-20.
[53] Lundkvist Josenby A, Jarnlo GB, Gummesson C, Nordmark E. Longitudinal construct validity of the GMFM-88 total score and goal total score and the GMFM-66 score in a 5-year follow-up study. Phys Ther. 2009;89:342-50.
[54] Oeffinger D, Gorton G, Bagley A, Nicholson D, Barnes D, Calmes J, et al. Outcome assessments in children with cerebral palsy, part I: descriptive characteristics of GMFCS Levels I to III. Dev Med Child Neurol. 2007;49:172-80.
[55] Hurn J, Kneebone I, Cropley M. Goal setting as an outcome measure: A systematic review. Clin Rehabil. 2006;20:756-72.
[56] Kiresuk T, Smith A, J. C. Goal attainment scaling: application, theory and measurement. New York: Lawrence Erlbaum Associates; 1994.
[57] Wagenaar N, Verhage CH, de Vries LS, van Gasselt BPL, Koopman C, Leemans A, et al. Early prediction of unilateral cerebral palsy in infants at risk: MRI versus the hand assessment for infants. Pediatr Res. 2020;87:932-9.
[58] Lin KC, Wang TN, Wu CY, Chen CL, Chang KC, Lin YC, et al. Effects of home-based constraint-induced therapy versus dose-matched control intervention on functional outcomes and caregiver well-being in children with cerebral palsy. Res Dev Disabil. 2011;32:1483-91.
[59] Li ST, Chiu NC, Kuo YT, Shen EY, Tsai PC, Ho CS, et al. Parenting stress in parents of children with refractory epilepsy before and after vagus nerve stimulation implantation. Pediatr Neonatol. 2017;58:516-22.
[60] Dong VA, Fong KN, Chen YF, Tseng SS, Wong LM. 'Remind-to-move' treatment versus constraint- induced movement therapy for children with hemiplegic cerebral palsy: a randomized controlled trial. Dev Med Child Neurol. 2017;59:160-7.

[61] Majnemer A, Shevell M, Law M, Poulin C, Rosenbaum P. Indicators of distress in families of children with cerebral palsy. Disabil Rehabil. 2012;34:1202-7.