PROTOCOL TITLE: Neuroplasticity Associated with Extended Daily Use of a Sensorimotor Priming Vibration System to Improve Hand Function After Stroke

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1.0 Objectives / Specific Aims

Aim 1: Determine the effect of in-home use of TheraBracelet on neural plasticity

- **Hypothesis*:*** TheraBracelet induces neural plasticity.

Aim 2: Determine the effect of in-home use of TheraBracelet on hand function

- **Hypothesis*:*** The immediate improvement in hand function with TheraBracelet leads to more use of the affected hand and arm in the home, resulting in hand functional recovery.

2.0 Background

More than 4 million stroke survivors in the U.S. suffer from post-stroke sensorimotor hand disability,[4] which is typically permanent and difficult to treat. Hand disability has a profound negative impact on functional ability and independence.[5, 6] One important roadblock to motor recovery is insufficient treatment for sensory deficits. Sensory feedback is integral to nearly all motor control tasks,[7, 8] and sensory deficits exacerbate motor deficits[9, 10] and hinder recovery.[11-13] The lack of a practical treatment approach for sensory impairment is a critical limitation to the current state of post-stroke hand rehabilitation. While sensory afferent stimulation has been shown to facilitate experience-dependent neural plasticity and motor recovery,[14-19] existing methods such as transcutaneous electrical nerve stimulation require a 1-2 hour application in a sedentary posture on a daily basis, which is impractical. To address this limitation and fully leverage the therapeutic benefits of sensory stimulation, we have developed “TheraBracelet” that delivers subsensory stimulation via a wearable wristband throughout daily living. It provides the dual benefits of facilitating plasticity and enabling home use to increase the treatment dose substantially beyond typical clinic visits available in the health care system.

TheraBracelet’s imperceptible random-frequency vibration helps other sensory signals from the hand exceed the threshold for sensing (known as stochastic facilitation[20]). The theoretical framework is that enhanced sensory feedback during everyday motor tasks will improve task performance, thus increase hand use in daily living, which will facilitate experience-dependent neural plasticity and hand motor recovery. Our preliminary research has identified an effective device design and a mechanism of action: 1) Immediate improvements in finger sensation[21] and dexterity[22] are observed by turning on the vibration. 2) The effective vibration intensity is 40% below sensory threshold, with higher intensities leading to lesser effects.[21, 23] 3) The vibration can be applied to the wrist because the same benefits were obtained for various vibration locations of the wrist, forearm, dorsum hand, and palm,[21, 23] and the wrist is optimal for a wearable device. 4) The mechanism for enhanced sensation is that TheraBracelet increases cortical sensorimotor network activity and conscious processing of the sensory signal, as evidenced by increased long-latency encephalogram (EEG) evoked potential for fingertip touch.[24]

3.0 Intervention to be studied

Intervention to be studied is wearing a device that can deliver TheraBracelet stimulation in daily living. The device will apply TheraBracelet stimulation (i.e., random-frequency vibration to the wrist at 60% of the sensory threshold determined using the staircase method) for the treatment group, and apply no vibration for the control group (placebo).

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

- Age = 18 or older
- At least 6 months post-stroke
- Fingertip touch sensory deficits as evidenced by the Semmes-Weinstein Monofilament Test score >2.83, 2-Point Discrimination Test score >5mm, or sense of numbness based on verbal report.
- Ability to move an object with the paretic hand
- Ability to put on a watch daily (by him/herself or with help)

Exclusion Criteria

- Complete upper limb deafferentation (complete upper limb numbness and no touch sensation from the Semmes-Weinstein Monofilament Test and the Two-Point Discrimination test)
- Rigidity (Modified Ashworth Scale=5)
- Upper limb botulinum toxin injection within 3 months prior to enrollment or during enrollment
- Brainstem stroke
- Comorbidity (peripheral neuropathy, orthopaedic conditions in the hand that limit ranges of motion, neurodegenerative conditions such as Parkinson's, Alzheimer, ALS, and MS, compromised skin integrity of the hand/wrist due to long-term use of blood thinners)
- Change in neurological disorder medications during the enrollment
- Concurrent upper extremity rehabilitation therapy
- Language barrier or cognitive impairment that precludes following 3-step instructions or providing consent

Contraindications to MRI and TMS include: pregnancy, epilepsy, history of brain tumor, hardware in the skull or spine (e.g., coils, clips) implantable medical devices (e.g., pacemaker), metal in the body (not compatible with MRI). Participants will still be eligible to participate if they present with any of these contraindications, however, they will be excluded from participating in these tests.

- **Screening**: Eligibility will be determined based on the potential participant's verbal disclosure or standardized clinical assessments. Potential participants will be asked to complete a pregnancy test.
- **Sex/gender:** We will include chronic stroke survivors of all genders and all racial and/or ethnic groups, since stroke occurs in persons of all genders and all racial and/or ethnic backgrounds. We will not exclude people based on sex/gender, racial or ethnic group.

Specifically, for sex, based on the demographic data and stroke surveillance data, approximately the same number of women and men will be recruited for this study. This recruitment is possible because we will recruit from the RESTORE stroke registry that has been developed by the CTTR Core and the RESTORE stroke registry has 48% female and 52% male stroke survivors.

- **Racial and ethnic groups:** Our goal is to construct a participant pool that matches post-stroke survivor distributions in South Carolina. Thus, we have considered the stroke prevalence in each racial and ethnic group together with the racial and ethnic distribution of the population in South Carolina and target enrollment of stroke survivors in each racial and ethnic group accordingly to represent the South Carolina stroke demographics. Recruitment of diverse racial an d ethnic groups is possible because the RESTORE stroke registry currently has 42% African-American and 1% Hispanic.
- **Children**: Children under the age of 18 years will be excluded. The rationale for exclusion of children is that stroke predominantly occurs in adults, and stroke is very rare in children. Importantly, these rare cases may actually differ in their etiology from the subjects we propose to study.

6.0 Number of Subjects

A total of 40 subjects will be recruited to participate in this study.

7.0 Setting

- All activities will be conducted in a Laboratory located on the Medical University of South Carolina campus.

8.0 Recruitment Methods

- Subjects will be recruited through the MUSC Registry for Stroke Recovery that has information of 838 stroke survivors who have agreed to be contacted for research (RESTORE, approved MUSC IRB PRO# 37803, Adams PI). The registry is growing every day, as approximately 500 new stroke cases are treated at the MUSC Stroke Center every year. All eligible stroke patients in the inpatient stroke units as well as the outpatient clinic are contacted by a dedicated recruiter of the Center to be enrolled in the registry. In addition to recruiting stroke survivors from the hospital, we recruit stroke survivors from the community by having a dedicated outreach therapist from the Center visit local stroke support group meetings and develop relationships with stroke survivors, caregivers and clinicians, and also by organizing community outreach events such as stroke caregiver summits and stroke recovery community engagement, to establish grassroots connections with stroke survivors and caregivers in the community. The Center also sends newsletters to survivors, caregivers, local clinics and local clinicians to inform them of news, new events and new projects. With this effort, the registry has been growing with >10 new enrollees per month.

- In addition to the registry, advertisement via internet (e.g., South Carolina Research Studies Directory) will be used.

9.0 Consent Process

- Consent will be obtained by the study personnel. The consent process will take place in a private room when the potential participant comes to the laboratory on a scheduled time agreed upon between the study personnel and the participant. The content of the consent will be verbally explained to the participant and the participant will be asked to raise any questions and concerns. If the person requests a waiting period, then one will be given. If the person desires to consent immediately, then the person will provide consent immediately.
- For participants who are having a modified protocol due to COVID-19, they will e-consent. Verbal instruction and explanation will be provided over the phone.

10.0 Study Design / Methods

- Study design: The study design is a double-blinded randomized controlled study. Subjects will wear the device for at least 8 hours/day every day during their normal activity for a month, during which they will come to the laboratory for weekly evaluation. Subjects will affix the device to the affected wrist using the unaffected hand, similar to wearing a watch. Follow-up evaluation will occur 3 months after. During this time, subjects will not receive other hand therapy. All subjects will be educated at each visit on the importance of using the paretic hand as much as possible in daily living. The device will deliver vibration (treatment) or no vibration (control) all the time. Double-blinding is possible because the treatment vibration is imperceptible (i.e. subthreshold).

  - Schedule: Participation in this study will last approximately 4 months. Subjects will come to the laboratory a total of 6 to 9 times. The baseline (1-2) visit will entail the baseline evaluation followed by an introduction to using the device. Then, weekly visits will be for evaluation after using the device for 1, 2, and 3 weeks. The post evaluation (1-2 visits) will occur after using the device for 4 weeks. The follow-up evaluation (1-2 visits) will occur after they stop using the device for 3 months. The baseline, post, and follow up evaluations may be completed in two visits in an effort to reduce fatigue among participants.

  - Evaluation: Multi-modal evaluation will be performed as detailed below.

  - MRI: One MRI assessment will be performed at baseline. The scan will be 20 minutes in duration. The MRI assessment is to obtain the individual participant's brain anatomy to facilitate subject-specific localization of brain activity.

  - EEG: For the EEG assessment, participants will wear an EEG cap on their head. Gel will be applied to individual EEG electrodes with a blunt syringe that does not penetrate the skin (taking approximately 30 min for this preparation). During the assessment, the participant will rest comfortably in a chair and either rest or grip with the fingers. The EEG assessment will take place at baseline, post, and follow-up evaluation session and last approximately 40 minutes including preparation.

  - Neural plasticity assessment: Participants will sit on a chair and rest. A TMS coil will be placed on top of the subject's head. The TMS coil location will be moved around slightly to find the 'hotspot' that stimulates neurons with direct monosynaptic projections to the

alpha motoneurons in the spinal cord for the abductor pollicis brevis (APB) muscle, as seen by the evoked potential in the APB (recorded using electromyogram, EMG) immediately after TMS, To record this MEP from the APB muscle, subjects will have the surface EMG electrodes on the skin on top of the APB muscle belly. Noninvasive electrical nerve stimulation will be applied to the participant's wrist via a surface electrode pair, immediately prior to the TMS. This assessment will take place at each evaluation session and last approximately 30 minutes.

- Clinical Assessment: Subjects' clinical upper extremity function scores will be assessed using conventional clinical assessments used in occupational/physical therapy in which participants will be asked to move the affected hand and arm, grasp objects and perform prescribed tasks (e.g., lifting an object off the table, releasing the object into a bin) as quickly as possible. These tests will be videotaped for scoring. The clinical assessments will take place at each evaluation session and last approximately 30 min.

- Biomechanical hand grip control assessment: Subjects will grip an instrumented object, lift the object off a table against gravity, steadily hold the object at a comfortable reaching distance for 5 s, and then slowly and intentionally release the grip until the instrumented object falls. Subjects will repeat this grip-lift-hold-release task 5 times. The biomechanical assessment will take place at baseline, post, and follow-up evaluation session and last ~15 minutes.
- Wear time assessment. Subjects will fill out a self-reported device use log, indicating the time at which they put on and take off the device every day in their home. They will submit the log to study personnel during the weekly visits.
- In-home upper limb use amount assessment. This assessment entails participants wearing accelerometers on both wrists using standard wrist straps for 3 days at baseline, immediately after one month of wearing TheraBracelet, and at follow-up. Subjects will be instructed to wear the accelerometers during the entire day. The wear time assessment will take place at each evaluation session.
- Home therapy program. Participants and their caregivers will meet with study staff to identify specific hand/arm tasks to practice at home. The goal of this program will be to increase hand/arm use in activities of daily living. Participants will document their progress on check-off sheets and submit them during their weekly laboratory visits.

- Due to COVID-19, some participants may be assessed over the phone only, and may continue with the home intervention (home exercise and watch) while being monitored via weekly phone calls until they could come to the laboratory for full assessments.

12.0 Data Management

- Analysis: The primary analysis will be a repeated measures ANOVA for each outcome. The primary independent variables are group (treatment vs. control), evaluation time (baseline and 1-4 weeks of using the device for the primary analysis; follow-up will be included in subsequent analysis), and their interaction. We will also include sex as an independent variable along with its interactions.

- Sample size justification: For the repeated measures design with a significance level of 0.0125 (adjusted for multiple comparisons), at least 80% power, and 5 primary time points, using a standard deviation of 6.4 s and compound symmetry correlation of 0.92 (observed in the pilot study), a sample size of 17 per group will be adequate to detect a minimum difference (futility level) of 7 s. Adjusting for 15% attrition, 20 per group is planned.
- Confidentiality: All data except for the consent forms and HIPPA forms will be de-identified at the time of data recording. All electronic data will be stored in a password-protected research server that is accessible to study personnel only. The server is backed up every day and maintained 24/7 by IT specialists. All paper data with personally identifiable information including the consent forms and HIPPA forms will be stored in a key-locked cabinet in a key-locked room that is accessible to study personnel only. Other paper data without personally identifiable information including testing sheets documenting testing sequences and notes will also be stored in a cabinet in a key-locked room that is accessible to study personnel only.
- Data sharing: Only de-identified coded data will be reported and/or shared with the public and other investigators in publications, in ClinicalTrials.gov, or via network storage.

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

The proposed research is a single site pilot clinical trial that is concerned with an intervention using an investigational device in a double-blinded randomized controlled design. A Data Safety Monitoring Board (DSMB) will be used.

- A DSMB will ensure the safety of participants and the validity and integrity of data collected during the tenure of the project. The overall framework involves review of the enrollment/retention and safety and adverse event data by the DSMB during the proposed research.

- DSMB composition: The DSMB will be composed of three professionals with expertise related to the proposed area of study who are not involved with the study design or experiments. Specifically, the DSMB will include: (1) a board-certified stroke neurologist who also is a stroke recovery researcher and is experienced in care of chronic stroke survivors and their recovery; (2) a registered and licensed occupational therapist who also is a quantitative researcher in outcomes measurement and research design; and (3) a biostatistician with expertise in design and analysis of clinical trials. This multidisciplinary group has experience with management and monitoring of clinical intervention trials involving individuals following stroke, and brings substantial expertise adequate to serve as the DSMB.

- DSMB responsibilities: The responsibilities of the DSMB are as follows.
  - Prior to any enrollment, the DSMB will review the study design, protocol, informed consent documents, amendments, recruitment/enrollment plan, statistical analysis plan, and data and safety monitoring plan, and document the agreement or recommendation.

- Once the enrollment begins, the DSMB will convene every 6 months to review the progress of the trial.
- The DSMB will review the enrollment/retention data including new enrollments, progression of the enrollees' participation in the study, any discontinuation of participation in the study with or without adverse events, and the current enrollment status compared to the project time line.
- The DSMB will review data quality and quality control data.
- The DSMB will review safety and adverse event data. The DSMB will review the aggregated summary data as well as the individual participants' data (de-identified). The DSMB will discuss participant risk vs. benefit and other factors that may potentially affect study outcomes. The DSMB will make recommendations for appropriate action to maintain a reasonable safety profile for the study.
- The DSMB will ensure that all serious adverse events have been followed to resolution, and that the appropriate agencies (including the IRB and/or federal funding agency) have been informed.
- The DSMB will advise the IRB and the study investigators as to whether the protocol should continue as scheduled or undergo any modification due to findings from the monitoring process. The DSMB may recommend stopping the study early if the study has unanticipated safety concerns that warrant stopping.
- The DSMB will review study performance as well as make recommendations and assist in resolution of problems reported by the PI.
- The DSMB will ensure the confidentiality of the study data and the results of monitoring.
- The DSMB will document their reviews in writing and provide a report to the IRB to summarize oversight activities, recommendations and any concerns regarding participant safety. The report will include participant characteristics (including distributions across race and sex), retention and disposition of study participants, quality assurance issues and reports of adverse events, significant/unexpected adverse events and serious adverse events.
- The DSMB will review final analysis results upon completion of the data collection.

- Reporting of safety data: All serious adverse events will be reported to the IRB as they occur. All enrollment/retention data, and safety and adverse event data will be reported to the DSMB during the review. The DSMB will review the data and submit a report to the IRB. Summative safety data will be reported to ClinicalTrials.gov, and in publications. As such, we will register this study in ClinicalTrials.gov as soon as the study commences and report results including all adverse events as soon as the study is completed following the guidelines. To protect participants' confidentiality, personally identifiable information will not be used for reporting. Only de-identified or aggregated data will be used for reporting.

14.0 Withdrawal of Subjects (if applicable)

- Subjects who do not show up on scheduled visits may be withdrawn by the investigator.
- For those who voluntarily withdraw from the research, their data collected up to that point may be used by the investigator.

15.0 Risks to Subjects

- There is a slight risk for loss of confidentiality although researchers will take appropriate steps to protect any information collected about the participants. There is a minor risk of physical and mental fatigue from engaging in the study activity. There is a minor risk of skin irritation from wearing the wristband. There is a minor risk of discomfort in moving the arm/hand while wearing a device on the wrist, although the TheraBracelet device weighs only 40 g.

- EEG: There is a minor risk of discomfort in wearing a head cap attached with a bundle of wires. Also, the gel used for the electrodes will get hair messy.

- TMS/electrical nerve stimulation: There is a serious risk that TMS could move iron-containing objects in or around the face or head, which in the process could possibly harm the person. There is a slight risk of a seizure with TMS; the incidence of seizures is very low and mostly associated with high frequency repetitive TMS (rTMS) which will not be used in this study. Instead we will use single-pulse TMS, which is much safer. There is a minor risk of scalp discomfort and headache. A TMS stimulus may feel like a slight tap to the skull. There may be discomfort from the muscle contraction that occurs in the hand muscle in response to the TMS. There is a very low risk of hearing loss due to the clicking sounds that the TMS machine makes. Safety of TMS in pregnancy is unknown. The electrical nerve stimulation will produce sensation on the wrist, which may cause discomfort. The use of tape or other adhesives to secure electrodes for EMG measurement and/or for electrical nerve stimulation during testing may cause some mild skin irritation. Subjects with contraindications (e.g., epilepsy, concussion, metal in the head/neck, pregnancy) will not be tested for TMS. Subjects will be screened for safety before administering TMS (e.g., removal of all loose metal objects like earrings or nose rings).

- MRI: There is a serious risk that MRI could move iron-containing objects in the MRI room, which could in the process possibly harm the person. The 3T MRI scanner is unsafe for pregnancy. There is discomfort by claustrophobia and by the loud banging noise. Temporary hearing loss has been reported from the loud noise from the MRI machine. The person may also feel uncomfortable as s/he will be asked not to swallow for a while. Subjects with contraindications (e.g., metal in the body such as a fragment in the eye, aneurysm clips, ear implants, spinal nerve stimulators, a pacemaker, or an implant electrical device, claustrophobia, pregnancy) will not be tested for MRI. Subjects will be screened for safety before entering the MRI room (e.g., removal of all loose metal objects like earrings or nose rings).

- There is a minor risk that subjects feel discomfort from wearing the accelerometer devices on their wrists for all day.

- Potential risks that might be associated with use of wrist vibration for a prolonged time include wrist skin irritation, increased upper limb pain, increased spasticity, weakness, and worsening of hand sensation or dexterity. These risks are expected to be rare because the intensity of vibration used in TheraBracelet is subliminal while we are exposed to higher-intensity, suprathreshold vibration daily (e.g. from a phone, car). Currently there is no vibration exposure guideline for this small level of vibration, as the

U.S. Occupational Safety and Health Administration provides vibration exposure guidelines only for high-intensity vibration such as jackhammers and hand-held powered drills. Currently there are no known side effects using this small imperceptible (unfelt) level of vibration used in the proposed study. TheraBracelet has been used for at least 8 hours daily for a month in chronic stroke survivors without safety concern in our pilot study. Nonetheless, safety of using TheraBracelet will be systematically monitored. Potential risk also includes discomfort of wearing a device on the wrist everyday.

16.0 Potential Benefits to Subjects or Others

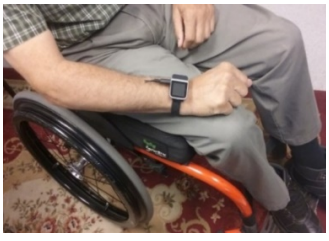
- There may be no benefit from participating in this study. The potential benefit is that the vibration the participant receives may help recover their hand function, although this cannot be guaranteed. The knowledge regarding the potential of using unperceivable vibration to enhance upper extremity physical recovery is important to improve hand function and activities of daily living for people who had a stroke and may benefit stroke survivors in general. The risks are deemed reasonable in relation to the potential gain of knowledge regarding this technology's efficacy in enhancing recovery of hand function after stroke.

17.0 Sharing of Results with Subjects

- If the subject agrees, the data collected and generated from this study will be shared to the Registry for Stroke Recovery (RESTORE-Pro#00037803) by the subject's registry ID. Sharing data from this study with the registry will allow for more targeted recruitment efforts in the future and allow researchers at MUSC to have a more complete registry with key stroke recovery elements including common data and physical function characteristics that are applicable to multiple studies. MUSC researchers and collaborating facilities will be able to query data sets to learn more about recovery of subjects after their stroke through institutionally managed secure servers that will assure HIPAA privacy and security compliance.

18.0 Drugs or Devices (if applicable)

- Device: A stand-alone prototype is composed of an MP3-playing watch and a vibrator (see the pictures below; total weight 40g, watch=3.7cm×5.3cm). Both items are off-the-shelf products (i.e. available to purchase for anyone). The vibrator is attached to the wristband of the watch. The vibrator's wire is connected to the MP3 player via an audio jack. The MP3 player drives the vibrator with its internal battery, enabling a full day of use after an overnight charge. The MP3 player/watch is charged using a conventional phone charger. The MP3 player can play any file including the treatment vibration file with white noise vibratory signal at the intensity that is 40% below the sensory threshold (i.e. subthreshold, imperceptible to the participant) and control file with zero amplitude (i.e. no vibration).

- FDA: The use of the vibrator for this proposed purpose of affecting the hand sensation and/or dexterity has not been approved by the FDA.
- The vibrators and watches will be stored in the laboratory and will be provided to the participants by the study personnel.

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