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Study Title: Brain functional connectivity & sensory stimulation-enhanced therapy post stroke

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PROTOCOL TITLE: Brain functional connectivity & sensory stimulation-enhanced therapy post stroke

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1.0 Objectives / Specific Aims

- **Aims:** To determine if the change in brain functional connectivity after one treatment session is associated with individual patients' response to treatment
- **Hypotheses:** Change in resting state brain functional connectivity after the first session is significantly associated with gains in motor function after completion of all treatment sessions

2.0 Background

Stroke is a major problem for modern society, affecting more than one new US citizen every minute.[1] Stroke is a heterogeneous disease, with high inter-subject variability associated with both baseline motor impairment[1] and response to interventions.[2-4] We have recently developed a novel intervention for post-stroke hand rehabilitation, named TheraBracelet, which uses vibrotactile sensory stimulation to increase proprioception during conventional upper extremity task-practice therapy. In our pilot study, we demonstrated a large effect size of TheraBracelet increasing upper extremity function after therapy compared to therapy alone. However, our data also show high between-subject variability in patient outcomes, an observation in line with most treatments for individuals in the chronic phase.[3,4] We aim to improve efficacy of neurorehabilitation by selecting patients who are likely to recover from our specific intervention, and assigning other patients to different therapeutic programs. However, there is a lack of tools to predict whether a specific subject will benefit from a specific treatment.

3.0 Intervention to be studied (if applicable)

Intervention is standard occupational therapy (i.e., subjects try activities of daily living with their hand and arm such as trying to open a jar) while the person wears a TheraBracelet device. The therapy is 1-2 hours/session, 3 sessions/week for 6 weeks.

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 for at least 22 hours, enabling a full day of use after an overnight charge. The MP3 player/watch is charged using a conventional phone charger. The vibrator is a general-purpose vibrator, not specifically designed for any particular purpose. The MP3 player will play white noise vibratory signal at the intensity that is 40% below the sensory threshold (i.e. subthreshold, imperceptible to the participant). Currently there is no vibration exposure guideline for this small level of vibration. People are exposed to higher-intensity, suprathreshold vibration daily (e.g. from a phone, riding a car).

FDA: Use of this device for this protocol has been determined as non-significant risk (NSR) and exempted from IDE by the FDA (please see the enclosed letter from the FDA).

5.0 Inclusion and Exclusion Criteria/ Study Population

Individuals will be screened for eligibility using clinical assessments, including Fugl-Meyer Assessment of Sensorimotor Function and Monofilament Test, that will determine upper limb motor impairment and sensory deficits.

Inclusion Criteria

- Age = 18 or older
- At least 6 months post-stroke
- Moderate upper limb impairment with the ability to participate in hand task practices
- Fingertip touch sensory deficits (e.g., Monofilament>2.83, 2-point discrimination>5mm, sense of numbness, tingling)

Exclusion Criteria

- Complete upper limb deafferentation
- Rigidity (Modified Ashworth Scale=5)
- 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, premorbid neurologic conditions, compromised skin integrity of the hand/wrist due to long-term use of blood thinners)
- Concurrent upper extremity rehabilitation therapy
- Language barrier or cognitive impairment that precludes following instructions or providing consent
- MRI incompatible.

- Screening: Eligibility will be determined based on the potential participant's verbal disclosure.
- Inclusion of Women and Minorities: We will include chronic stroke survivors of all genders and all racial and/or ethnic groups that are representative of the demographics of Americans who had a stroke. We will not exclude people based on sex/gender, racial or ethnic group. Specifically, according to data from the 2013 Behavioral Risk Factor Surveillance System, BRFSS (CDC), 2.7% of men and 2.7% of women $\geq$ 18 years of age had a history of stroke. Thus, approximately the same number of women and men will be recruited for this study. Also, according to the same data, 2.5% of non-Hispanic whites, 4.0% of non-Hispanic blacks, 1.3% of Asian/Pacific Islanders, 2.3% of Hispanics of any race, 4.6% of American Indian/Alaska Natives, and 4.6% of other races or multiracial people had a history of stroke. Thus, considering the stroke prevalence in each racial and ethnic group from the BRFSS together with the racial and

ethnic distribution of the American population from the 2010 U.S. Census, we will target enrollment of stroke survivors of all racial and ethnic groups accordingly.

- Exclusion of Children: We will recruit individuals who have had a stroke at least 6 months ago, who are 18 years old or older. 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.

6.0 Number of Subjects

- A total of eight 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

- Study participants will be recruited from our Registry for Stroke Recovery that has information of 680 stroke survivors stroke who have agreed to be contacted for research (RESTORE, approved MUSC IRB PRO# 37803, Adams PI). In addition to the registry, advertisement via internet (e.g. South Carolina Research Studies Directory) will be used.

9.0 Consent Process

- 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.

10.0 Study Design / Methods

- Study design: A single cohort study. Describe what subjects will do. Subjects will receive 6-week standardized task-practice therapy with TheraBracelet on their affected wrist (2 hr/d, 3d/wk, 18-session). Clinical assessments will be performed at baseline, after each week of therapy, and at 1-month follow-up. Change in brain FC during rest before vs. after the first therapy session will be assessed using fMRI and EEG independently.
- Schedule: Participation in the study will last approximately 10 weeks. Participants will visit the laboratory 3 times a week for 6 weeks (18 sessions) to receive treatment. Additionally, participants will visit the laboratory for 3 assessment visits (before and after the treatment intervention and at one-month follow-up).

- MRI: MRI assessments will be performed two times, before and after the initial therapy session. The first scan will be for 1 hour. The second scan will be for 30 minutes. Subjects will rest on a scanner bed and either rest or press buttons with the fingers for the first scan while their resting or task fMRI is obtained. In addition to fMRI, structural MRI scan will be obtained for the individual participant's brain anatomy.
- 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 approximately 0.5 hour to complete, in addition to the 30 min prep time.
- Clinical Assessment: The clinical assessment will include measurement of the hand function scores using the Wolf Motor Function Test, Box and Block Test, and Action Research Arm Test, and completion of a patient-centered outcomes questionnaire on self-reported abilities for activities of daily living using Stroke Impact Scale hand subscale. For the hand function scores, participants will move the affected hand, grasp objects, and perform prescribed tasks (e.g. lifting the object off the table, releasing the object into a bin) as quickly as possible. These tests will be videotaped for quality control purposes. These tests will be scored by a therapist. For the patient-centered outcomes questionnaire, Stroke Impact Scale hand subscale will be administered through pen-and-paper administration. The questionnaire is to assess if the hand functional improvement translates to self-reported abilities for activities of daily living. Additionally, acute responsiveness to vibration will be assessed for all subjects by repeating measurement of the sensory and motor scores of the Monofilament Test and Box and Block Test while the device delivers vibration. The clinical assessment will take approximately 1 hour to complete.
- Protection against risk: For fatigue, frequent and sufficient breaks will be provided to participants. Fatigue and pain will be monitored using a visual analog rating scale administered immediately before and after each therapy or assessment session. Depending on the change in the fatigue/pain rating, the therapy tasks to be practiced will be graded in terms of its difficulty to reduce excessive fatigue and pain (i.e. If the participant experiences finger joint pain, s/he may try gross grasping as opposed to finger individuation. If the participant experiences shoulder pain, s/he may lower the reaching target or object location to reduce shoulder flexion requirements). The comfort will be maximized by using cushions, adjusting table or chair heights, adjusting the back rest, using a foot rest, etc.

  For potential skin irritation due to wearing the wristband, the wristband tightness may be adjusted or a new wristband may be tried to maximize participant comfort. For the EEG assessment, the gel used for the electrodes can be washed off with shampoo. The participant will be advised to bring a hat to wear for the way home.

  For the MRI, all participant receiving MRI are required to complete a screening questionnaire to ensure that the person does not have any loose metal objects such as earrings or nose rings or a piece of 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. Persons with potential for pregnancy will be excluded. Each person

will be screened before each MRI assessment. To prevent hearing loss, the participant will be asked to wear earplugs and headphones for MRI.

Potential risks that may be associated with use of wrist vibration (wrist skin irritation, increased upper limb pain, increased spasticity, weakened grip strength, worsening of hand sensation, and worsening of hand dexterity) will be systematically assessed at all times (for evaluation time points including after each week of continuous therapy and 1-month follow-up, as compared to baseline) as safety data. Negative changes in these safety measures will be communicated to the participant immediately and be explained. In addition, any other adverse events regardless of whether it is related to the device or not will be explicitly asked and recorded at all evaluation time points as well as any time they occur. All of these safety data and adverse event information, in addition to the daily safety screening and fatigue/pain monitoring data, will be reported to the DSMB, IRB, clinicaltrials.gov, and in publications.

Participants will be notified if we learn anything that might make them change their mind about participating in the study. Participants will be informed that they can drop out of the study at any time without penalty.

11.0 Data Management

- Analysis: we will test if the clinical outcome is associated with change in FC after one session (representing motor memory consolidation activity) by constructing a linear regression model.
- Sample size justification: This is a pilot study with n=8. We target to complete data collection for 4 subjects.
- 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.

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

The proposed research is a single-site pilot proof-of-concept clinical trial that involves an intervention of standardized task-practice therapy combined with an investigational device. A Data Safety Monitoring Board (DSMB) will be used. The primary purpose of the DSMB is to ensure the safety of participants and the validity and integrity of data collected during the study. 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 (1) a board certified stroke neurologist who is also a stroke recovery researcher, is a Director of the Post-Stroke

Spasticity Clinic, and is experienced in care of chronic stroke survivors and their recovery; (2) a registered and licensed occupational therapist who is also a quantitative researcher in outcomes measurement and research design; and (3) a biostatistician with expertise in design and analysis of clinical trials. The three individuals bring substantial expertise adequate to monitor data and safety for this stroke recovery intervention clinical trial.

- DSMB responsibilities: The responsibilities of the DSMB are as follows. Prior to any enrollment, the DSMB will review the study design, protocol, recruitment/enrollment plan, statistical analysis plan, and data and safety monitoring plan, and document the agreement or recommendation. After the enrollment begins, the DSMB will convene to review the enrollment data, and the safety and adverse event data (see below for detailed data description) at the end of the study, unless an adverse event occurs in which case the PI will inform the DSMB immediately and the DSMB will review the incidence at that time. The DSMB will review the aggregated summary data as well as the individual participants' data (de-identified). The DSMB will provide recommendations for any safety concerns. The DSMB may recommend stopping the study early if the intervention has safety concerns. The DSMB will review the results and document their reviews in writing. In summary, the stopping rules are if the study has unanticipated safety concerns that warrant stopping. The DSMB will also provide a report to the IRB to summarize oversight activities, recommendations, and any concerns regarding participant safety.

- Data to be reviewed by DSMB: Two types of data will be reviewed by the DSMB.
    1. Enrollment/retention data: Enrollments, progression of the enrollees' participation in the study, and any discontinuation of participation in the study with or without adverse events will be reviewed.
    2. Safety and adverse event data: At every visit, participants' safety will be monitored in the following procedure. For daily safety screening, each participant's blood pressure and heart rate will be assessed upon their arrival to the laboratory. Abnormal level, compared to their baseline, will trigger consulting with the study clinician, rescheduling the visit, or seeking medical attention by calling the participant's doctor and/or sending the participant to the emergency room especially if severe headache and blurry vision are experienced. This daily screening will be documented.

       For safety monitoring during each visit, we will monitor pain and fatigue on a visual analog scale prior to beginning and immediately after each therapy or assessment session. This information, in comparison to baseline, will be used to grade task activity to prevent excessive pain or fatigue in patients during therapy (i.e. If the participant experiences finger joint pain, s/he may practice tasks involving gross grasping as opposed to finger individuation. If the participant experiences shoulder pain, s/he may lower the reaching target or object location to reduce shoulder flexion requirements). During assessment, comfort will be maximized using cushions or adjusting a foot rest, table height, back rest, etc. Excessive pain or fatigue that cannot be modified will lead to termination in the participation in this research study.

       Safety of using the TheraBracelet device will be assessed at each evaluation time point. Effects of using TheraBracelet on hand function scores (the Wolf Motor

Function, Box and Block, and Action Research Arm scores) are assessed after each week of therapy and at 1-month follow-up, compared to baseline. In addition to the hand function scores, broad aspects of safety will be systematically assessed at all evaluation time points for all participants as part of clinical assessments. These safety data will include any wrist skin irritation (verbal report and/or visual examination), increased upper limb pain level (on a visual analog pain rating scale from 1 to 10), increased spasticity (on the Modified Ashworth Scale), weakened grip strength (using Jamar grip dynamometer), and worsening of hand sensation (using the Semmes-Weinstein Monofilament Test score), compared to baseline. Decline will be considered as an adverse event if a reasonable criterion is met: if the participant exhibits wrist skin irritation that did not exist prior to the invervention, if the pain level increases by more than 2 points, if the Modified Ashworth Scale increases by more than 1 level (equivalent to the effect size of botulinum toxin A), if grip strength declines by more than 20% from the baseline which is approximately 2 standard deviation of the population data, if the Monofilament Test declines by one category (e.g. "normal" to "diminished light touch") with a change of more than two points, and/or if the hand function scores decline by more than the larger of the minimum detectable change and the minimal clinically meaningful difference reported in literature. Negative changes in these measures will be communicated to the participant immediately and be explained. A potential need for medical attention will be discussed.

Any adverse events, regardless of whether it is related to the device or not, will also be explicitly asked and recorded at all evaluation time points. These safety assessments will add additional 10 minutes to the clinical assessment at each evaluation time point.

All daily safety screening, pain/fatigue, and safety/adverse event information will be recorded de-identified (coded). Coded paper documents will be stored in a locked cabinet in a locked office, and coded electronic data will be stored in a password-protected research server. They will be accessible to only study personnel. All daily screening, pain/fatigue, and safety/adverse event data will be tabulated for each time point. All adverse events will be summarized in terms of frequency, severity, and relatedness to the study intervention using the Medical Dictionary for Regulatory Activities code (MedDRA).

Reporting of safety data: All 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.

13.0 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.

14.0 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.

- For the EEG assessment, 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. For the 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.

- 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 during hand task practice therapy in chronic stroke survivors for a total of 12 hours without any adverse events including no skin irritation in our pilot study. In addition, the investigators have used TheraBracelet vibration for 12 hours/day every day for 1 month continuously with no safety issues, including no skin irritation. Nonetheless, safety of using TheraBracelet will be systematically monitored.

15.0 Potential Benefits to Subjects and 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. Another potential benefit is that the hand therapy the participant receives may help recover their hand function, although this cannot be guaranteed. The knowledge regarding the potential of using unperceivable vibration as a therapy booster 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.

16.0 Sharing of Results

- 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.

17.0 Drugs or Devices

- The vibrators and watches will be stored in the laboratory and will be provided to the participants by the study personnel.

References

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