Medical University of South Carolina
Protocol

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Study Title: Sensory Stimulation to Enhance Hand Function Post Stroke

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TABLE OF CONTENTS

A. SPECIFIC AIMS

The *objective* of this pilot project is to assess the impact of the novel sensory vibration stimulation technique we have developed in enhancing outcomes of hand therapy as well as the central nervous system responsiveness in chronic stroke survivors. This impact will be assessed in a double-blind stratified randomized controlled trial for stroke survivors. The *hypothesis* is that improvement in hand function will be greater for the experimental group receiving the wrist subthreshold vibrotactile stimulation during therapy compared with the control group who will wear the device with no vibration (placebo), and that this better improvement in hand function is associated with neurophysiologic measures of central nervous system responsiveness.

B. BACKGROUND AND SIGNIFICANCE

Stroke survivors suffer from persistent hand impairment that diminishes their functional abilities and independence, despite multiple courses of rehabilitation. Sensory stimulation can prime central excitability to increase therapy outcome. Unlike existing methods including transcutaneous electrical nerve stimulation, muscle/tendon vibration, and repetitive transcranial magnetic stimulation (TMS) that require prior exposure to the sensory stimulation as long as 2 hours before each therapy session, we developed a new sensory stimulation technique that has the potential to immediately prime the central sensorimotor system for the hand, using imperceptible vibration applied to the wrist skin. Wearable devices with a vibrating function are low cost and can be easily adopted for rehabilitation purposes to impact a wide range of patients with sensorimotor impairment. In addition, this subthreshold vibrotactile stimulation is unique compared to the traditional stochastic resonance, by stimulating the wrist while improving fingertip tactile sensation. This remote approach exposes the entire hand to receive relevant sensory information and improve the ability to successfully manipulate objects. Despite the potential for clinical benefits and easy adoption for high impact, knowledge about the long-term efficacy of this new sensory stimulation technique and its underlying mechanism is limited. This limitation presents an obstruction to clinical adoption and optimization for efficacy.

C. PRELIMINARY STUDIES

The PI's preliminary studies showed that hand motor scores immediately improved with remote subthreshold (unperceivable) vibrotactile stimulation. Stroke survivors completed the Nine-Hole Peg and Box and Block tests faster with subthreshold (60% of the sensory threshold) vibrotactile stimulation applied to the wrist ($p<.05$) (Seo et al. 2014). The stimulation was generated by Tactor (EAI, Casselberry, FL) placed on the skin using tape. Learning effects were controlled by practice and pseudo-randomizing the stimulation off and on. Improvement in hand motor function with the stimulation was seen not only in stroke survivors but also in healthy adults (Hur et al. 2014).

Preliminary studies also showed that tactile sensation improved with the stimulation. Instantaneously with the stimulation, stroke survivors could detect smaller Semmes-Weinstein monofilaments on the fingertips, indicating improved touch sensation ($p<.01$) (Enders et al. 2013).

D. RESEARCH DESIGN AND METHODS

The hypotheses will be tested in a double-blind stratified randomized controlled trial. Experimental and control groups will be compared for post-therapy changes in hand function. To obtain two comparable groups, stroke subjects will be stratified by their initial hand motor and sensory scores (Fugl-Meyer and Semmes-Weinstein mild vs. moderate). Subjects will be randomly and blindly assigned to either the experimental or the control group. A standardized task-practice therapy focused on dexterous object manipulation and multi-joint upper extremity coordination will be used, since the intervention targets sensory feedback-based motor control. The research therapists at the SC Stroke Recovery Research Center have been trained in its implementation and routinely use this protocol. Each subject will receive therapy two hours/day, 3 days/week for 2 weeks. The duration of 2 weeks is deemed sufficient to result in statistically greater improvement in motor outcome and cortical reorganization (seen using fMRI/TMS) for the experimental compared to the control group. The two groups will receive therapy of equal intensity individually in the same room supervised by the same therapist who is blinded to the group and does not know how the coin-sized device providing the light vibration works. Tactor (EAI, Casselberry, FL) generating light vibration in our preliminary studies will be applied to the wrist. At the beginning of each therapy session, the subject's sensory threshold will be determined and the vibrating intensity will be adjusted to either 60% of the sensory threshold or zero, depending on the group. Blinding to the light vibration stimulation is possible because subjects cannot perceive subthreshold (imperceptible) vibration, thus they do not know whether they are receiving the vibration or not.

Evaluation will be performed before (pre-intervention testing), after (post-intervention testing), and 2 weeks after the therapy (follow up testing). Clinical sensorimotor function of the hand will be assessed using clinical tests, such as the Nine Hole Peg, Action Research Arm, Box and Block test to assess dexterity, as well as the Semmes-Weinstein and Grating Orientation tests to assess sensation. Secondarily, the Stroke Impact Scale and Stroke-Specific Quality of Life Scale will be recorded to assess the potential for the light vibration stimulation to impact patients' self-care abilities. Neurophysiologic evaluation will be performed using the MRI including an anatomical scan, diffusional kurtosis imaging (DKI), and functional MRI (fMRI) during grip, TMS including resting and active motor thresholds and motor evoked potential peak-to-peak amplitudes (all of these variables are routinely used in MUSC TMS evaluation protocols), and EEG evoked potentials and frequency power modulation during grip.

Each subject will visit MUSC for a total of 9 to 12 times over a period of a month. The pre-intervention testing will include screening, clinical hand function assessment, MRI, TMS and EEG. There will be six therapy visits lasting 2 hours each. Post-treatment evaluation will include clinical hand function assessment, MRI, TMS, and EEG after the completion of therapy. Follow up testing will include clinical hand function, TMS, and EEG again 2 weeks after the completion of therapy. Each set of evaluations (pre, post, and follow up testing) can be performed over 2 days to minimize participant fatigue.

Subjects will be paid $100 total per set of evaluations. For pre- and post-testing, the participant will receive $25 for each type of evaluation completed (i.e., clinical hand function, MRI, TMS, and EEG) for a total of $100. For follow-up evaluations, the participant will receive $33 for clinical hand function, $33 for TMS, and $34 EEG for a total of $100. The participant will receive $25 per therapy visit for participation in this study. There will be a total of 11 evaluations sessions and 6 therapy visits. If they complete all evaluations and therapy visits, they will receive a total of $450. If they stop participating in the study, they can keep the payment they have already received, but will not receive any more compensation. If the subject does not complete one of the assessments due to scheduling conflicts or safety risks (see Section 2.b.), the subject will not receive remuneration for that portion of the study. The payment will be in cash, at the end of each visit.

Analysis: Repeated measures ANOVA with post hoc comparisons will be used to determine if each clinical hand function score improves more for the experimental compared with the control group. A significant interaction between time (pre, post, 2 weeks after) and group (experimental/control) will support the hypothesis. Pearson's correlations between the mean change in clinical hand function scores and each of the neurophysiologic measures will be examined to identify relevant neurophysiologic measures for hand function.

Expected Outcomes: Greater recovery of dexterous hand function is expected with the light vibration stimulation (with a significant session×group interaction). This exciting finding will be the first to demonstrate that this unperceivable vibration stimulation at the wrist improves hand therapy outcomes.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

1. The subject will complete safety screening including presence of any metal in the body, history of epilepsy, and concussion.
2. The level of hand and arm movement as well as fingers' touch sensation will be assessed. For movement assessment, the subject will be asked to move the hand and arm in specific ways as best as one can and move objects in different sizes and shapes around the table with the hand as quickly as possible. For sensation assessment, the subject will be asked if s/he can feel a small touch on fingertips.
3. If the subject is eligible for the study, the subject will be randomly assigned to one of two groups. This means that the subject has a 50/50 chance (like flipping a coin) of being in either group. Neither the researchers nor the subject will make the choice of which group to which the subject is assigned. The two groups are Group A (unperceivable wrist vibration group) and Group B (placebo, no wrist vibration group).
4. For both groups, we will ask the subject about the stroke type (ischemic or hemorrhagic) and location as much as the subject knows.

5. For both groups, we will perform four types of evaluations to measure recovery. The assessment of the hand/arm movement ability and finger sensation will serve as evaluation #1 (clinical hand function). Evaluation #1 may take an hour.
6. In addition, the subject will have a Magnetic Resonance Imaging (MRI) exam (evaluation #2). This MRI exam includes an anatomical scan to specify the area of the brain that we will stimulate using transcranial magnetic stimulation (TMS) for the next evaluation, DKI that provides information about the architecture within the cortex relevant to revealing lesion-specific impairment, and fMRI to examine brain networks used during hand grip. For the MRI exam, the subject will lie down on a narrow bed which will then be placed in a tunnel that is 6 feet by 22 inches wide and open at each end. the subject will lie there quietly for about half an hour, during which time the subject will hear a loud noise. The subject may feel warm during this procedure. Evaluation #2 will take approximately an hour.
7. Next, excitability of neurons in the brain will be assessed using TMS (evaluation #3, TMS). TMS is a noninvasive brain stimulation device. We will help the subject put an elastic cap onto the head. This cap is like a swimmers cap. The subject will be asked to sit in a cushioned chair and asked to be at rest or hold a light grip while the brain receives stimulation. A TMS pad will be held above the head. The tester will trigger a switch on the TMS paddle which will deliver a magnetic pulse to the outside of the skull. The subject will hear a clicking sound when the paddle produces its magnetic energy and the subject might feel a light tap against the scalp. The magnetic pulse stimulates the brain nerves controlling the hand. Therefore the subject may or may not feel the hand muscle briefly twitch depending on the strength of the TMS pulse. The subject might also feel the facial muscles twitch slightly just around the eye. This twitch is a result of the TMS directly stimulating the facial nerves and muscles that run directly under the scalp. The TMS pad may be moved around the head until the best position is located to give a contraction of the hand muscle. This contraction will be measured by a muscle activity sensor that will be placed on the hand skin with a sticky pad and/or tape. Evaluation #3 may take a half an hour.
8. For the fourth evaluation, the subject will wear a cap weaved with electrodes on the head. The electrodes will have gels on them and the gels can make hair messy. So the subject may be advised to bring a hat to wear after this session. The subject will be seated and either receive light touches on the fingertip at rest or pinch at a light force (as in holding a pen) upon cues, while brain activity is recorded using the electrodes of electroencephalogram, EEG (evaluation #4, EEG). Evaluation #4 may take two hours.
9. After completing all evaluations, both groups will receive upper limb therapy 3 times a week for 2 consecutive weeks (for a total of 6 sessions) while wearing a vibrator at the wrist. An off-the-shelf mechanical vibrator in the size of a dime will be used. During therapy, Group A will receive vibration at the wrist at the level that is imperceptible. Group B will receive placebo, also in zero vibration at the wrist, during therapy. Both groups will not feel any vibration at the wrist during therapy, because the vibration is either very small or none. The therapy will focus on object manipulation, dexterous hand movement, and coordinated hand and arm movements.
10. After the last therapy session, all four evaluations (hand clinical function, MRI, TMS, and EEG) will be performed again.
11. Two weeks after the last therapy session, the subject will come to MUSC again to go through the three evaluations again (hand clinical function, TMS, and EEG).

Thirty chronic stroke survivors will be recruited (with 15 in each of the control and experimental groups). The age range will be 21 and older.

The inclusion criteria are mild to moderate impairment in upper extremity function (approximately 30 to 60 on the Fugl-Meyer Upper Extremity without the reflex portion). Exclusion criteria are cognitive dysfunction as evidenced by inability to follow three-step instructions and/or provide consent to participate in the study, stroke<3 months (to avoid interference with acute care), treatment with botox in the affected arm within 3 months of start of study, and age <21. Individuals with MRI contraindications (e.g., metal in the body, claustrophia, pregnancy) or TMS contraindications (e.g., history of seizure, concussion, pregnancy) may still be considered for the study, but will not complete the contraindicated evaluation. Inclusion is based on clinical assessment, because recovery relates most with initial impairment level, not lesion characteristics.

Targeted/Planned Enrollment Table

Total Planned Enrollment: 30

TARGETED/PLANNED ENROLLMENT: Number of Subjects

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	2	2	4
Not Hispanic or Latino	13	13	26
Ethnic Category: Total of All Subjects*	30		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	4	8
White	10	10	20
Racial Categories: Total of All Subjects*	15	15	30

Stroke survivors are the target subjects as the intervention under investigation targets to improve rehabilitation outcomes of stroke survivors.

Children are not recruited because stroke is rare in children.

b. Sources of Materials

Recorded data are hand clinical function assessment scores, brain MR imaging data, electromyogram signal data obtained during the TMS session, electroencephalogram signal data obtained during the EEG session, subject characteristic information of gender, age, time since stroke (years and months), stroke type/location (obtained by asking each person), and consent/HIPPA forms. All data are collected specifically for the proposed research project.

All data except the consent/HIPPA forms will be de-identified and labeled by subject codes. The linkage between the subject identities and subject codes will be accessible to the study personnel only.

c. Potential Risks

1. There is a slight risk for loss of confidentiality although researchers will take appropriate steps to protect any information collected about the subjects.

2. Randomization: The treatment one person receives may prove to be less effective or to have more side effects than the other study treatment.

3. Imperceptible vibration: For people in the group that receives vibration at the wrist, prolonged vibration may numb although it is very unlikely because the vibration applied is very small to the extent that it is imperceptible.

4. TMS: TMS could move iron-containing objects in or around the face or head, which could in the process possibly harm the person. There is a slight risk of a seizure with TMS. There is a very low risk of scalp discomfort and headaches. 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 use of tape or other adhesives to secure EMG sensors during testing may cause some mild skin irritation.

5. MRI: MRI could move iron-containing objects in the MRI room, which could in the process possibly harm the person. There is discomfort by claustrophobia and by the loud banging noise. Temporary hearing loss has been reported from the loud noise. The person may feel uncomfortable as s/he will be asked not to swallow for a while.

6. EEG: It may be uncomfortable to wear a head cap attached with a bundle of wires during evaluation. Also, the gel used for the electrodes will get hair messy.

7. Unknown Risks: The experimental treatments may have unknown side effects.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Stroke survivors will be recruited from the MUSC stroke research registry database (approved MUSC IRB PRO#15991, Kautz PI) at the MUSC College of Health Professions Center for Rehabilitation Research in Neurological Conditions. The database currently contains contact information for ~200 persons with stroke who have signed informed consent to be contacted for research. In addition, the SC Research Directory will be used for recruitment.

Recruitment
This study will recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803), which is a registry with subjects consented for future contact. RESTORE staff will query the registry for potential subjects and provide the Principal Investigator (PI) with the contact information of subjects who meet their criteria. The PI or research staff will contact subject to further screen for potential enrollment.

Sharing Data
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.

The consent process will take place when the potential participant comes to the laboratory on a scheduled time agreed upon between the study coordinator and the participant. The content of the consent will be verbally explained to the subject and the subject 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.

b. Protection against Risk

1. Loss of confidentiality: Appropriate steps will be taken to protect any information collected. The data from test results will be de-identified once it has been collected and before it is stored. This means individual results would not be able to be linked to the subject by others who review the results of this research. The linkage between subject codes and identities as well as all other identifiable information including consent/HIPPA forms will be stored in a locked room and be accessible only to the study personnel.

2. TMS: The MUSC Brain Stim Laboratory requires that all subjects receiving TMS and MRI complete a screening questionnaire to ensure that the person does not have any loose metal objects like 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. A person must be screened before each TMS and/or MRI exam. Persons who do not meet the screening criteria for TMS or MRI may still be considered eligible for the study, but will not complete these evaluations.

The primary safety concern with TMS is the induction of seizures; however, the incidence of seizures is very low and mostly associated with high frequency repetitive TMS (rTMS) which will not be used in this project. Instead we will use single-pulse TMS, which is much safer and we will follow published "gold standard" safety guidelines for diagnostic TMS to minimize the risk of inducing a seizure *(Groppa et al. 2012)*.

Hearing protection for all subjects during TMS will be provided. Stimulation sessions will be stopped immediately with any complaints of discomfort or for any complaints of dizziness or light-headedness. There are no lower-risk methods available to gain the same scientific information.

A TMS stimulus may feel like a slight tap on the skull. There is a very low risk of scalp discomfort. The subject will be asked to notify the experimenter if s/he experiences these. The headache or changes in cognitive function is expressed, the subject will stop participating in the study.

Persons with potential for pregnancy will not have the TMS stimulation. Persons with a history of seizures will not have the TMS stimulation.

For mild skin irritation related to the use of tape or other adhesives to secure EMG sensors during testing, the subject will be advised to clean the adhesive residue with either alcohol swab provided or soap and water after the experiment.

5. MRI: The MUSC Brain Stim Laboratory requires that all subjects receiving TMS and MRI complete a screening questionnaire to ensure that the person does not have any loose metal objects like 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. A person must be screened before each TMS and/or MRI exam. To prevent hearing loss, the subject will be asked to wear earplugs. Persons who do not meet the screening criteria for TMS or MRI may still be considered eligible for the study, but will not complete these evaluations.

6. EEG: The gel used for the electrodes can be washed off with shampoo. The subject will be advised to bring a hat to wear for the way home.

7. Unknown Risks: Subjects will be notified if we learn anything that might make them change their mind about participating in the study.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There may be no benefit from participating in this study. The potential benefit is that the therapy the person receives may help gain hand function, although this cannot be guaranteed. The small vibration may prove to increase the therapy outcome than the therapy itself without vibration or than other available treatments, although this cannot be guaranteed. The knowledge regarding the potential of increasing the therapy outcome using unperceivable vibration as well as the underlying mechanisms is important to increase quality of life of 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 the effectiveness of this small vibration in improving therapy outcomes, potential benefits of the therapy itself, and effects on central nervous systems.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Currently hand rehabilitation therapy outcomes are unsatisfactory for many patients with stroke. The knowledge regarding the potential of increasing the therapy outcome using unperceivable vibration as well as the underlying mechanisms is very important to increase quality of life of people who had a stroke.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

The TMS and MRI safety screening by the MUSC Brain Stim Laboratory will be performed before each testing and recorded. All adverse effects/events and any protocol deviations will be documented on a case-report form and will be reported to the IRB at the time of the event. To protect participants' confidentiality, the subject code will be used. Personally identifiable information will not be used for reporting. All study records and data will be kept in a locked area and be accessible only to the study personnel. Persons who do not meet the screening criteria for TMS or MRI may still be considered eligible for the study, but will not complete these evaluations.

F. REFERENCES/LITERATURE CITATIONS

Seo, N.J., Kosmopoulos, M.L., Enders, L.R., Hur, P. (2014). Effect of Remote Sensory Noise on Hand Function Post Stroke, *Frontiers in Human Neuroscience*, Nov 17; 8:934.

Hur, P., Wan, Y.-H., Seo, N.J. (2014). Investigating the role of vibrotactile noise in early muscle reaction to perturbation, *IEEE Transactions on Biomedical Engineering*, 61 (6):1628-33.

Enders LR, Hur P, Johnson MJ, Seo NJ. Remote vibrotactile noise improves light touch sensation in stroke survivors' fingertips via stochastic resonance. *J Neuroeng Rehabil*. 2013;10:10

Groppa, Oliviero et al, A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. Clin Neurophysiol. 2012;123:858-882

G. FACILITES AVAILABLE

The therapy and movement assessment will be conducted by research therapist at the SC Stroke Recovery Research Center in the College of Health Professions Upper Extremity Motor Function Rehabilitation and Assessment Laboratories (UE Labs) which are directed by Dr. Woodbury. The UE Labs are housed on the 2nd Floor of the CHP Research Building (77 President Street) the home of the Center for Rehabilitation Research in Neurological Conditions, and the COBRE funded Stroke Recovery Research Center. The MRI exam (evaluation #2) will be conducted at the Center for Biomedical Imaging on 33 Bee St. The evaluation #3 involving the transcranial magnetic stimulation (TMS) will be conducted in the Neurostim laboratory adjacent to the upper extremity laboratory on 77 President St. The evaluation #4 involving the electroencephalogram (EEG) will be conducted in the EEG laboratory adjacent to the upper extremity laboratory on 77 President St.