PROTOCOL TITLE:
Concomitant sensory stimulation during therapy to enhance hand functional recovery post stroke

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1.0 Objectives / Specific Aims

The objective of this proposal is to determine if combining vibration with hand task practice is superior to hand task practice alone in an adequately powered study.

Aim 1: To determine clinical potential of vibration in improving hand functional recovery
Hypothesis: Improvement of hand motor function will be greater for the treatment than control.

Aim 2: To determine the effect of vibration on sensorimotor grip control and neural communication
Hypothesis: The treatment will enhance sensorimotor grip control via strengthened neural communication for hand grip, compared with control.

2.0 Background

Post-stroke hand impairment is highly prevalent, persistent, and difficult to treat. Hand impairment has a profound negative impact on functional ability and independence.[1, 2] One way to improve treatment efficacy is to augment therapy with peripheral sensory stimulation.[3] Afferent input is a powerful driver of change in the motor cortex.[4-6] Sensory stimulation in conjunction with therapy has been shown to improve motor outcomes more than therapy alone.[3] While promising, most modalities of sensory stimulation interfere with natural hand tasks, because suprathreshold electrical stimulation causes tingling sensation[7, 8] irrelevant to tasks at hand, and wearing of a glove or a finger cap hampers dexterous finger movement and causes a sense of discomfort.[9, 10] Thus, most modalities of peripheral sensory stimulation are administered prior to therapy, requiring additional time commitment. These constraints make it difficult for patient adherence and implementation.[11]

To address these practical limitations and fully leverage the potential therapeutic benefits of sensory stimulation, we have developed a new stimulation that is imperceptible random-frequency vibration applied to wrist skin via a watch. We determined the optimal stimulation parameters (location, intensity, and frequency) based on our experimental data[12, 13] and literature.[14-25] The theoretical framework is that imperceptible random-frequency vibration stimulates mechanoreceptors in wrist skin and afferents,[26, 27] adds small random currents to neurons in the sensorimotor cortex, triggering coherent[16] firing[18] at the peak of inputs related to hand tasks, and consequently enhances neural communication[15, 28] for hand tasks[14] and functional recovery. Our pilot data support the theoretical framework by demonstrating that neuronal firing magnitude and coherence in the cortical sensorimotor network for hand tasks increased with vibration vs. without, as measured by electroencephalogram (EEG). In addition, preliminary efficacy has been demonstrated in two pilot studies. First, use of vibration during 2-wk task-practice therapy resulted in greater improvement in manual dexterity assessed by the Box and Block Test (BBT) than dose-matched therapy alone, which sustained at follow-up (19 days post intervention).[29] Second, use of vibration during 6-wk task-practice therapy resulted in greater mean improvement in movement time assessed by the Wolf Motor Function Test (WMFT) compared with 10-wk task-practice therapy[30] and 12-wk manual therapy[31] alone both at post and follow-up evaluations.

3.0 Intervention to be studied

Intervention to be studied is standardized hand task practice therapy (1-2 hours/session, 3 sessions/week for 6 weeks) with a watch (Fig 1) worn on the paretic wrist only during the therapy sessions. The watch is equipped with a vibrator and will apply vibration for the treatment group, and no vibration for the control group during therapy. The treatment vibration signal is adjusted to be imperceptible to the participant.

The use of watch vibration for the purpose of improving hand function has not been approved by the FDA, but has been approved as a nonsignificant risk device under the IDE regulation by the FDA. Use of the vibration for this purpose was safe in our previous pilot trial.[29]

Fig 1

4.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

- 18 years old or older
- At least 6 months post stroke
- Wolf Motor Function Test (WMFT) total average time >10 s and hand task average time <120 s

Exclusion Criteria

- Currently undergoing other upper limb therapy
- Change in spasticity medication or upper limb botulinum toxin injection within 3 months prior to or during enrollment
- Severe spasticity that limits participation in task practice therapy (e.g., Modified Ashworth Scale=4-5)
- Complete upper extremity deafferentation
- Comorbidity affecting the upper limb function such as orthopaedic conditions limiting motion, premorbid neurologic conditions, premorbid peripheral neuropathy, compromised skin integrity of the wrist due to burn or long-term use of blood thinners, or significant neurological symptoms from interview-based screen for new symptoms similar to stroke and its worsening and severity
- Language barrier or cognitive impairment that precludes following instructions and/or providing consent

People with contraindications to MRI and/or TMS will participate in the study, but not complete the MRI and/or TMS. 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 that is not compatible with MRI.

Screening: Eligibility will be determined based on the potential participant's verbal disclosure or standardized clinical assessments. To minimize travel and face-to-face contact, video screening may also be used using HIPAA-compliant video applications (e.g., Microsoft Teams).

Plan to include a diverse population: 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. Our goal is to construct a participant pool that matches post-stroke survivor distributions in South Carolina, based on the stroke prevalence data in each sex, racial and ethnic group together with the sex, racial and ethnic distribution of the population in South Carolina. Recruitment of diverse groups is possible, because the RESTORE stroke registry currently has 48% female, 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.

5.0 Number of Subjects

A total of 76 subjects will be recruited to participate in this study.

6.0 Setting

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

7.0 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). In addition, a chart review will be conducted for research purposes. Potentially eligible patients will be identified. We will submit a Research Data Request to obtain a recruitment report of MUSC patients who potentially meet eligibility criteria. The potentially eligible patients who have agreed to be contacted for future research by logging their MUSC Research Permissions preferences in MyChart will be contacted by phone, letter, or email and invited to participate. Other patients who did not update their MUSC Research Permissions in MyChart may also be cold-contacted by phone, letter, or email to be informed of the study if it is appropriate. We will not cold-contact any patients who have chosen to opt-out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment. In addition to the registry, advertisement via internet (e.g., South Carolina Research Studies Directory) will be used.

8.0 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.

9.0 Study Design / Methods

Study design: The study design is a double-blinded randomized controlled study. Participants will undergo standardized hand task practice therapy (3 sessions/week for 6 weeks) with the watch worn on the paretic wrist. Participants will be randomized into two groups: The device will deliver vibration for the treatment group and no vibration for the control group during therapy. Half the participants will be in the treatment group, and half in the control group. Double blinding is possible since treatment vibration is imperceptible (i.e., subthreshold). Evaluation will be performed at baseline, after 2, 4, and 6 weeks of continuous task practices and at 1-month follow-up.

Schedule: Participation will last 2.5 months. Participants' involvement entails 18 visits for therapy (each lasting 1-2.5 hours, 3 sessions/week for 6 weeks) and 2 evaluation visits (evaluations at each time point divided into 2 visits to minimize fatigue) for each of the 3 time points (baseline, after therapy, and follow-up), along with one time only, 30-min MRI assessment, resulting in a total of 25 visits over 2.5 months. Each activity is described below.

Therapy: Participants will undergo a standardized hand task-practice therapy program. Upper limb tasks for activities of daily living that are of the participants' interests and are related to participants' goals will be chosen and practiced with repetitions, in the laboratory. The difficulty level of the tasks will be modified per participants' progress. To translate improved motor capacity to independence at home, the paretic hand use in daily tasks at home will be tracked and encouraged.

Evaluation: Each of the two evaluation visits will last approximately 2-5 hours. The following assessments will be performed across the two evaluation visits.

Upper limb function assessment: 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 or at a comfortable speed, upon cues. These tests

will be videotaped for scoring. Position sensors will also be placed on the participant's upper limb using tape and be recorded. Participants will also complete a patient-centered outcomes questionnaire regarding self-reported abilities for activities of daily living and perception of the intervention. In addition, participants will be instructed to wear accelerometers on both wrists using standard wrist straps for 3 days outside the lab.

Neural assessment: Evaluations using electroencephalogram (EEG), magnetic resonance imaging (MRI), and transcranial magnetic stimulation (TMS) will be performed. 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. During the assessment, the participant will rest comfortably in a chair and either rest or grip with the fingers.

TMS is used to locate the 'hand knob' of individual subjects functionally (vs. anatomically). The hand knob is the area in the precentral gyrus in the primary motor cortex that gives monosynaptic input to the hand muscles. The functional hand knob will be located using TMS, since it may have migrated out of the precentral gyrus through post-stroke reorganization. The functional hand knob will be identified by the 'hotspot' for the hand intrinsic muscle (APB) found using TMS if subjects are safe for TMS. 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 hand muscle, as seen by the evoked potential recorded using electromyogram (EMG) immediately after TMS. To record this from the muscle, subjects will have the surface EMG electrodes on the hand skin. TMS is administered to locate the hotspot, not as a treatment.

Additionally, one MRI assessment will be performed only one time during enrollment. 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.

10.0 Data Management

Recruitment: Recruitment projects are housed in REDCap. Only study personnel will have access to the REDCap database while actively enrolling for the study.

Analysis: The primary analysis will be a repeated measures ANOVA for each outcome. The dependent variables will be the change from baseline at the evaluation times. The primary independent variables are group, evaluation time, and their interaction. We will also include sex as a biological independent variable along with its interactions. If the group by time interaction is significant, we will examine if there is a group difference at 10 weeks using post-hoc tests.

Sample size justification: The clinically meaningful difference in time needed to complete a functional upper limb task is deemed to be 4 to 7 s. This study will be powered to detect difference at follow-up of at least 4s in movement time between the treatment and control groups. For the repeated measures design with a significance level of 0.017 (adjusted for multiple comparison), at least 80% power, and 4 time points, for a standard deviation (SD) of 5.1s and compound symmetry correlation of 0.92 (both based on our pilot study[29]), sample size of 32/group will be adequate. Adjusting for 15% attrition, 38/group is planned (total n=76).

Confidentiality: All data except for the consent forms and HIPPA forms will be coded 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. Videos of the upper limb movement will be recorded such that we will avoid capturing the participant's face, while capturing the hand, arm, and object being gripped. 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 data depository.

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

A DSMB will ensure the safety of participants and the validity and integrity of data collected. 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 researcher and is experienced in care of chronic stroke survivors and their recovery; (2) a registered and licensed occupational therapist who also is a researcher; 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.

12.0 Withdrawal of Subjects

Subjects who do not show up on scheduled visits or do not complete the intervention in 10 weeks may be withdrawn by the investigator. Subjects who are or become medically unstable may be withdrawn by the investigator. For those who withdraw from the research, their data collected up to that point may be used by the investigator.

13.0 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 watch. There is a minor risk of discomfort in moving the arm/hand while wearing a watch on the wrist. There is a minor risk that subjects feel discomfort from wearing the accelerometer devices on their wrists for all day.

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: 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 use of tape or other adhesives to secure electrodes during testing may cause some mild skin irritation. Subjects with contraindications (e.g., epilepsy, 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).

Potential risks that might be associated with use of wrist vibration 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 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 level of vibration used in the proposed study. This vibration 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 will be systematically monitored at every visit.

14.0 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. 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 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 and its associated neuroplasticity.

15.0 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.

16.0 Drugs or Devices

The device is a custom-developed watch with a vibrator.

The device will be stored in the laboratory and will be provided to the participants by the study personnel.

Use of the watch vibration for the purpose of improving hand function has not been approved by the FDA, but has been approved as a nonsignificant risk device under the IDE regulation by the FDA.

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