COMIRB Protocol

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Project Title: Vibrotactile Stimulation for Neurological Disorders
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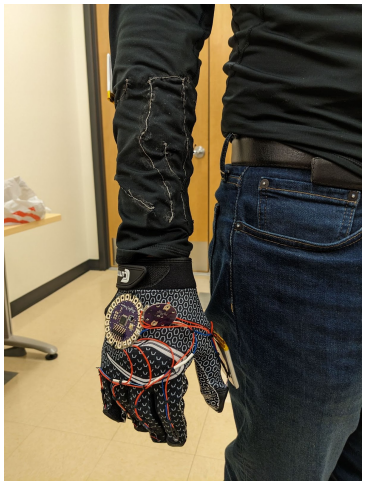
I. **Hypotheses and Specific Aims**:

In this pilot study, we will determine the feasibility and gain information on the effect size and variability of a rehabilitation therapy for stroke with wearables that stimulate the impaired upper extremity through a randomized control trial with 24 subjects. Subjects will be randomized 1:1 to a therapy group (vibrotactile stimulation in addition to conventional therapy) and a control group (conventional therapy alone). We have designed a shirt and glove that applies vibrotactile stimulation on the upper extremity. Subjects will wear the shirt for 45 minutes daily and the glove for 45 minutes daily during their stay a CU Anschutz inpatient rehabilitation unit. Subjects expected to stay at least 1 week at the unit (as assessed by their occupational therapist or physician). Our primary outcome measure is the Fugl-Meyer Upper-Extremity Assessment. Secondary outcome measures include the Modified Ashworth Scale, the Thumb localization test and a questionnaire to determine how the wearable is tolerated by the subjects and to assess their experience with the therapy. Testing will be conducted at baseline and discharge from the inpatient rehabilitation unit. *We hypothesize that the therapy group will have greater improvements in upper-extremity motor function, spasticity, tactile perception and range of motion compared to the control group after vibrotactile stimulation and that the device will be well-tolerated by patients.*

II. **Background and Significance**:

Nearly 17 million people worldwide have a first stroke each year (Feigin et al. 2014). Up to 80% of stroke survivors experience upper-extremity impairments such as spasticity, weakness, abnormal muscle activity patterns, and limited tactile perception and range of motion (Dobkin & Dorsch 2011). Impairment of the upper extremity is often chronic and a cause of long-term disability (Ward 2017). Despite this, studies indicate that in our current rehabilitation model, patients spend a low amount of time in therapy doing rehabilitation exercises (Lang et al. 2009) as our current rehabilitation model is largely clinic-based and resource-intensive. This stands in contrast with the evidence that indicates that high-intensity rehabilitation, early after stroke and over a sustained period is critical to maximize recovery (Hayward et al. 2021). Wearable technology has the potential to mitigate the limitations of our current rehabilitation model.

There is growing interest for non-invasive stimulation for the treatment of neurological disorders. Repeated upper-extremity muscle vibration has been shown to improve motor function and reduce spasticity in laboratory and clinical settings (Annino et al. 2019, Calabro et al. 2017, Marconi et al. 2011). It is hypothesized that the improvements associated with vibrotactile stimulation are partially due to primary afferent input that induces a functional restoration of inactivated, but preserved motor pathways and a rearrangement of motor cortical maps (Marconi et al. 2011). There is preliminary evidence that indicate that vibrotactile stimulation from a glove can help patients recover from stroke, by reducing spasticity, increasing tactile sensitivity and improving range of motion, yielding clinically important improvements (Seim et al. 2021, Seim et al. 2023). This will be the first study to investigate the effects of vibrotactile stimulation in the upper extremity with a wearable device. Given that post-stroke spasticity is common on the muscles of the upper and lower arm (Thibaut et al. 2013), our device has the potential to yield further improvements than a stimulation limited on the knuckles (Seim et al. 2021). The cost of





the wearable device (approximately $80) could allow the widespread adoption of the therapy.

III. Preliminary Studies/Progress Report:

We have developed a device that applies vibrotactile stimulation on the upper extremity and hand. The vibration motors (Seeed Technology Ltd, manufacturer number: 316040001) have frequencies that vary between 100-250Hz and amplitudes between 0.5-1.5g. These small motors are placed on the patient's body through gloves and shirts (see picture below). We have 5 motors on the fingertips and 18 motors on the upper extremity.

IV. Research Methods

A. Outcome Measure(s):

The primary outcome measures is the Fugl -Meyer Upper-Extremity Assessment (FM-UE), which consists of a set of movements such as shoulder flexion/extension and elbow flexion/extension. The form with this assessment is found here: https://www.gu.se/sites/default/files/2021-01/FM-UE%20eng%20190303%20PROTOCOL.pdf. This assessment is reliable (Gladstone et al. 21) and consists of 33 items graded on a scale from 0 to 2, with a maximum score of 66. Secondary outcome measures include the modified Ashworth scale, which is used to assess spasticity and tests the resistance to passive movement about a joint with varying degree of velocity. The instructions for the modified Ashworth scale are described here: https://www.sralab.org/sites/default/files/201706/Modified%20Ashworth%20Scale%20Instructions.pdf. Another outcome measure is a questionnaire for the subjects to determine how they tolerated wearing the device for the duration of the therapy. Tactile perception will be evaluated with the Thumb localization test. In this test, the subject has their eyes closed, and the examiner positions the impaired limb in fixed positions, and asks the subject to pinch the thumb with the opposite thumb and index finger (Otaka et al. 2020).

B. Description of Population to be Enrolled:

The inclusion criteria for our study are that patients must be between 50 and 70 years old, have a unilateral left or right sided ischemic stroke within the previous 2 weeks, have Upper-Extremity Fugl-Meyer scores between 0 and 58 and are expected to stay at least 1 week in the rehabilitation unit (as assessed by their occupational therapist or physician). Patients that suffer from cognitive impairments after stroke will consent with the help of their caregivers or family members, ensuring that they have understood and agreed to participate in the study. Patients will be excluded if they are involved in other clinical trials or under anti-spasticity therapy. Patients with communicable diseases and "yellow gown isolation" patients like C. Diff or MRSA will be excluded because of the added difficulty and concern with disinfecting the device. Patients that are dependent on pacemakers, have defibrillators, have lymphedema or AV fistula for dialysis on an arm will be excluded.

C. Study Design and Research Methods

Subjects that have suffered a stroke and that stay in the inpatient rehabilitation unit at CU Hospital or at Broomfield Hospital will start wearing the vibrotactile stimulation shirts and gloves for the duration of their stay at the rehabilitation unit. We will conduct some testing at the rehabilitation unit at baseline (typically day 2 after stroke) and at discharge (on average after 21 days). Testing will last at most three hours. The device will be stored within Al Borno lab storage space and will be sanitized with alcohol-based cleaner before giving them to subjects. We will hand-wash the shirts and gloves every 3 days (or more often if needed) and the vibrotactile motors will be sanitized with alcohol-based cleaner. The subjects can wear a thin shirt below the vibrotactile stimulation shirt. The battery in the device is rechargeable and we will recharge it every night. Subjects will wear the shirt for 45 minutes daily and the glove for 45 minutes daily during their stay at the inpatient rehabilitation unit (subjects will not wear the shirt and glove at the same time, so the total duration of the stimulation is 1.5 hours). Subjects do not need to have the stimulation be applied continuously throughout the day (i.e., they can take breaks from the stimulation by turning the device off). Subjects will be notified that the device will track usage time. No stipends will be provided to the subjects as this is an initial pilot study without external funding. Most subjects will wear the device between 3pm and 10pm, after completing their conventional rehabilitation therapy. A member of the research team will be present at the rehabilitation unit for the entire duration when a subject will be wearing the device. They will help the subject wear and remove the device whenever necessary (showers, defecations, etc.). The member of the research team will recharge the battery nightly. Dr. Nathan Odom or Dr. Mazen Al Borno will discuss our study with the nurses and rehabilitation unit staff to ensure that they are aware of our work. We will show the nurses how to remove the device and turn it off (but we expect that our research staff will do this work).

The standard of care for both groups consists of 3 hours of occupational therapy per day (usually finishes by 3pm daily), 5-7 days per week. Block randomization (block size of 6) generated by a computer program will be used to avoid bias. The randomization will be stratified according to baseline Upper-Extremity Fugl-Meyer score of 0 to 20 or 21 to 40. We will use a web-based database (Research Electronic Data Capture, REDCap) to conduct the randomization.

D. Description, Risks and Justification of Procedures and Data Collection Tools

The vibrotactile stimulation is similar to a phone gently vibrating. The device does not provide a significant risk. There is a minor risk of the wires of the device could get caught with objects in the environment. We will analyze the subjects' kinematics with computer vision technology (Kanazawa et al. 2019). There is a small risk of loss of confidentiality.

Storage and Management data will be conducted with our own in-house developed software (i.e., Python and MATLAB scripts to store text and json files, in our encrypted local drives). Data will be stored in local hard drives that are encrypted with CU Denver. Data will be backed-up in other local drives that will also be encrypted and placed in a locked room, with restricted access (only by a member of the research team).

E. Potential Scientific Problems:

One difficulty is to quantify the improvements in the outcome measures that are solely due to the vibrotactile stimulation, as opposed to endogenous recovery or placebo effects. It is also unknown how long the stimulation should be applied before we should expect to see effects.

F. Data Analysis Plan:

We plan on using a 2-sample t-test to estimate the mean changes in the outcome measures after treatment. We will recruit a total of 24 patients (12 patients in each group) through Dr. Nathan Odom at UC Hospital. We have chosen the sample size of our study based on a power analysis to detect the minimally clinically important difference (MCID) of 7 in the Upper-Extremity Fugl-Meyer score between the vibrotactile stimulation therapy and the conventional therapy. In the literature, the MCID is often considered to be 10% of the maximum score, that is 6.6 points (Gladstone et al. 2002, Krakauer et al. 2021). The 10 subjects per group provided 84% power (effect SD at 5) based on a 2-sample t-test with 2-sided α level at 0.05 (Krakauer et al. 2021). Our study will be conducted with 12 subjects per group to account for subject attrition. Each study participant will be randomized 1:1 independently to one of the two groups. This number of subjects is feasible because Dr. Nathan Odom sees 2-3 stroke patients weekly at CU Hospital or at Broomfield Hospital that satisfy our inclusion criteria. Our objective is to complete this pilot within two years.

G. Summarize Knowledge to be Gained:

Determination of the effects (e.g., on spasticity, range of motion, tactile sensitivity) of non-invasive vibrotactile stimulation on the recovery of upper-extremity movements after stroke. We will also have an assessment of how subjects tolerate wearing the device daily. This pilot study could provide the basis for a longer 8-weeks study in the stroke patient's home with the wearable device.

H. References:

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