Synchronized Brain and Hand Stimulation After Stroke

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SYNCHRONISED STIMULATION BRAIN AND HAND STIMULATION PROTOCOL

Study Design

We will employ a single group pre-post design. All the assessments including the ones used for screening are reliable and valid.

Inclusion criteria:

1) Male or female (either right or left handed) with unilateral hemiparesis after stroke;

2) Stroke onset of at least six months prior to the time of participation;

3) Ability to elicit motor evoked potential in the EDC muscle

4) Ability to grasp, as indicated by a score of at least 1 (out of 2) on the finger mass flexion and cylindrical grasp items of Upper Extremity Fugl-Meyer scale

5) age between 18-85 years

6) less than 20° active extension from the neutral position in the more-affected wrist and fingers

Exclusion criteria:

1) Presence of severe aphasia , measured by cognitive and/or language impairments that preclude the ability to follow simple instructions;

2) Excessive spasticity of wrist and finger muscles, defined as a Modified Ashworth Score more than or equal to 3, which may limit the ability to open the hand/fingers;

3) Diagnosis of neurological disorders other than stroke, which may confound the results;

4) Has touch and proprioceptive sensory deficits determined via a score of 0 on the position sense section (section H) of the Fugl Meyer Upper Extremity assessment proprioception, which may limit the ability to report excessive amount of tingling due to hand stimulation

5) History of seizure or epilepsy as the effects of TMS are not tested in individuals with

seizures or epilepsy;

6) Orthopedic/musculoskeletal conditions (e.g., arthritis) affecting the upper extremity, which may limit the ability to move the affected hand

7) Presence of metallic implants in the head or neck for TMS and/or pacemaker;

8) Currently or trying to become pregnant, as the effects of TMS are not tested in pregnant women;

9) Difficulty maintaining alertness or remaining still for MRI;

10) Ferromagnetic metallic implants, pacemakers, other implanted devices, or ventilators (for MRI);

11) Bodyweight > 300 lbs due to MRI scanner dimensions

12) Psychiatric diagnosis according to the criteria of the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V), or who are on psychotropic medication, which may confound the results

13) Cognitive impairments, defined as a score of < 23 on the Mini Mental Status Examination, which may limit the ability to follow the commands in the study

14) Excessive pain > equal to 5 on Visual Analog Scale in the more-affected upper extremity, which may limit the ability to participate in the study

15) History of schizophrenia, Bipolar disorder (type I or II) [Answer yes to questions 16 and items of the (hypo) maniac module of MINI], current moderate, severe depression (Scores of >10 on PHQ-9) and other neurological or medical conditions that could confound results.

16) Life expectancy less than the duration of the study

17) Hemispatial neglect, which may limit the ability to pay attention to the affected hand

18) Participating in concurrent therapy, which may confound the results

19) We will exclude children because although stroke may occur in children, the protocol is addressing stoke in adults and the devices are not approved for use in

children

20) Individuals getting Botox in the last 3 months. We will exclude individuals getting Botox in the last 3 months because Botox can potentially the muscles and may interfere with the findings (muscle activity) of the study.

Screening procedures

If the participant qualifies based upon the initial phone screen, we will obtain informed consent and perform a more detailed screen using the following procedures:

1) We will review potential participants' medical charts after obtaining informed consent to confirm they have a primary diagnosis of unilateral hemiparesis due to a single episode of stroke, are 18 years or older, and that their onset of stroke is at least 6 months prior to study screening, have no history of schizophrenia, other neurological or medical conditions that would confound results. The UPMC medical chart will be accessed through a secure network at the Keystone Building of the University of Pittsburgh.

2) We will conduct procedures to screen for excessive pain in the weak hand using the Visual Analog Scale.

3) We will also conduct a brief screen of sensorimotor abilities to determine if individuals are able to actively grasp objects with the weak hand using the Fugl-Meyer Upper Extremity Assessment (FMUE). This scale measures motor impairment by asking the participant to perform various arm and hand motions. This scale also measures impairments related to touch and proprioception sensations. Items are scored on a 3-point ordinal scale with 0 representing inability to complete the item and 2 representing ability to complete the item as asked.

4) We will also conduct a brief screen of upper extremity range of motion using a goniometer to determine if individuals have less than 20° active extension from the neutral position in the more-affected wrist and fingers.

5) We will ask participants to follow directions to determine whether they have the ability to follow 3-step commands.

6) We will also conduct a brief cognitive screen using Mini Mental Status Examination to screen for cognitive impairments which may confound the results of the study.

7) We will also conduct a brief mood screen using Patient Health Questionnaire-9 to

screen for more than mild depression and question 16 and items of the (hypo) maniac module of the Mini-International Neuropsychiatric Interview Hybrid Assessment to screen for bipolar disorders.

8) We will also screen for one side neglect or hemispatial neglect using the Line Bisection Test, which is a quick paper-pencil test.

9) We will conduct urine pregnancy testing for all women of childbearing potential prior to TMS.

10) We will also screen participants who do not show a motor evoked potential response of the finger extensor muscle with the transcranial magnetic stimulation. We will use a MagStim 2002 Magnetic Stimulator, and figure-eight 70 mm D coil (MagStim Ltd., Wales, UK) to stimulate the ipsilesional M1. Based upon standardized procedures the stimulating coil position and participant's head position will be recorded using a frameless stereotactic system (BrainSight, Rogue Research, Montréal, QC) and will be co-registered with the anatomical brain image obtained from the MRI scan. Stimulation will be guided by a 1-cm grid distributed anteroposteriorly and mediolaterally over the brain surface in BrainSight, initially centered over the hand knob of ipsilesional M1 (the posterior protrusion of the middle of the precentral gyrus). Surface EMG electrodes (Ag-AgCl) will be applied to the belly of the affected EDC muscle and a reference electrode will be placed at the clavicle. We will then use the TMS coil to stimulate the hand knob region in the ipsilesional M1 to identify a motor evoked potential from the EDC muscle using the EMG electrodes placed on the EDC muscle.

DETAILS OF THE SCREENING ASSESSMENTS (total participant time: 3 hours):

1) Visual Analog Scale (VAS):

The VAS quantifies the pain in the more-affected upper extremity using a 10 centimeter scale, with 0 representing no pain and 10 representing extreme pain. A cut off score of 5 or greater will be used.

2). Modified Ashworth Scale (MAS):

The MAS is a clinical measure of muscle tone and involves passive movement of the more-affected should, elbow, forearm, wrist and fingers.

3) Mini Mental State Examination (MMSE):

The MMSE is a clinical measure to examine cognitive status and the ability to follow commands and range from 0-30. A cut off score of more than 24 will be used.

4) Patient Health Questionnaire (PHQ-9):

The PHQ-9 rates the severity of 9 symptoms of depression on scale of 0 to 3. A cut off score of more than 10 will be used.

5) Mini-International Neuropsychiatric Interview Hybrid Assessment (MINI):
The question 16 and items on the (hypo) maniac module will be used to screen bipolar disorders. An answer to "yes" to the questions and items will indicate bipolar disorders.

6) Line Bisection Test (LBT):
Allows to screen patients with hemispatial neglect of the body.

All individuals who provide informed consent, complete screening procedures described above, and meet study criteria will participate in the study. The PI or personnel trained and supervised by the PI will perform the procedures.

IIa. INITIAL EVALUATION PROCEDURES (total participant time: 2 hours): Each participant will undergo the following evaluation procedures before starting each session of the synchronously paired M1 stimulation with FES-facilitated motor practice. These assessments will only be administered once.

The following assessments will be administered:

1. Descriptive Measures: Medical Record Review: We will collect demographic (age, gender, race, ethnicity, education, vocation, pre-stroke residential status and social support), medical (stroke etiology and onset, co-morbidities, medications) and rehabilitation history (type and duration) data from the medical record.

2. Imaging: Anatomical MRI imaging will be collected based on various recommended guidelines for transparency and fidelity in human brain imaging to enhance the rigor and reproducibility of the study. Participants will be screened for MRI safety. Brain imaging will be conducted using a 3T with 128-channel receivers (Prisma, Siemens Healthcare, Erlangen, Germany). Anatomical imaging will consist of T1 MPRAGE sequence (FOV:256mm, 1mmx1mmx1mm voxel size, TR=2.3s, TE=2.94ms) and 3D FLAIR (FOV:256mm, 1mmx1mmx1mm voxel size, TR=5s, TE=390ms). Images will be imported to the neuronavigation software (BrainSight), which will be used to localize ipsilesional M1 prior to the TMS session. MRI completion will take 1 hour.

The MRI will be performed either at the MRRC or the CMU-Pitt Bridge center. Depending upon the availability of the MRI site (MRRC or the CMU-Pitt Bridge center) and participant availability, participants will be scanned either at the MRRC or the CMU-Pitt Bridge center. This will provide us the ability to accommodate for the site schedule as well as participant availability.

EVALUATION PROCEDURES FOR AIM TESTING (total participant time: 3.5 hours each session):

Primary end-point: Motor performance (measured by percent change in the number of blocks in the Box and Block Test)

Secondary end-point: Use-dependent plasticity (measured by percent change in motor evoked potential of the extensor digitorum communis muscle) and Motor performance (measured by percent change in the maximum voluntary force production of the extensor digitorum communis muscle)

Each participant will undergo the following evaluation procedures pre (2.5 hours) and post (1 hour) each synchronously paired TMS-FES facilitated motor practice session on the same day. The testing after the synchronously paired TMS-FES facilitated motor practice session will take less time before we would have already identified the hot spot for the EDC muscle in the brain.

1. Transcranial magnetic stimulation to evaluate use-dependent plasticity: We will use a MagStim 2002 Magnetic Stimulator, and figure-eight 70 mm D coil (MagStim Ltd., Wales, UK) to stimulate the ipsilesional M1. We will use standardized procedures to enhance the rigor and reproducibility of the study. The stimulating coil position and participant's head position will be recorded using a frameless stereotactic system (BrainSight, Rogue Research, Montréal, QC) and will be co-registered with the anatomical brain image obtained from the MRI scan. Stimulation will be guided by a 1-cm grid distributed anteroposteriorly and mediolaterally over the brain surface in BrainSight, initially centered over the hand knob of ipsilesional M1 (the posterior protrusion of the middle of the precentral gyrus). Surface EMG electrodes (Ag-AgCl) will be applied to the belly of the affected EDC muscle and a reference electrode will be placed at the clavicle. The motor evoked potential (MEP) data will be collected by stimulating the targets in the grid at 2000 Hz with Signal software (CED, Cambridge, UK). The hotspot will be located for each participant by methodically stimulating each location in the grid over the representation of the more-affected hand in the ipsilesional M1. The "motor hotspot' will be identified within ipsilesional M1 as the site evoking MEPs of at least 100 μV peak-to-peak amplitude in slightly contracted affected EDC

(10%-20% of maximal volitional contraction) in at least 5 of 10 trials at the lowest TMS intensity.36 The intensity used to elicit criterion-level MEPs will be called active motor threshold (AMT).

Use-dependent plasticity: Use-dependent plasticity will be assessed by obtaining recruitment curves of the MEPs in the active state (10%-20% of maximal volitional contraction of the EDC muscle) at the “motor hotspot”. Ten serial MEPs will be collected at gradient increases in intensity ranging from 100 to 150% of the AMT. The order of the intensities will be randomized. We will compute area under the recruitment curve using the trapezoidal method to test Aim 1

2. Voluntary force production to evaluate motor performance: We will measure force production of the wrist and finger extensors (EDC) using two 34.09 kg load cells embedded in cushioned customized platforms. The height of the load cells can be altered to accommodate individual hand sizes. Participants will perform 5 trials of isometric wrist and finger extension movements against load cells for 10 seconds. The force data will be amplified by 5-20K and collected at 1000 Hz using Biopac amplifier and software (Biopac Systems Inc, Goleta, CA, USA). To allow for the deliberate increase to peak force as well as the tendency to drop off near the end of the 10-second interval, we will calculate force output over the central 5 second segment. We will use the median force as an overall measure of sustained performance and compute an average of the median force across five trials to test Aim 2.

3. Box and Block Test: The Box and Block Test (BBT) measures unilateral gross manual dexterity and the ability to release objects. It is a quick, simple and inexpensive test. It can be used with a wide range of populations, including clients with stroke. The BBT is composed of a wooden box divided in two compartments by a partition and 150 blocks. The BBT administration consists of asking the participants to move, one by one, the maximum number of blocks from one compartment of a box to another of equal size, within 60 seconds. The box is oriented lengthwise and placed at the client’s midline, with the compartment holding the blocks oriented towards the hand being tested. Participants first perform this test with their unaffected hand in order to practice and register baseline scores. Additionally, a 15-second trial period is permitted at the beginning of each side. Before the trial, after the standardized instructions are given to participants are advised that their fingertips must cross the partition when transferring the blocks, and that they do not need to pick up the blocks that might fall outside of the box. Participants are scored based on the number of blocks transferred from one compartment to the other compartment in 60 seconds. Each hand is scored separately. Higher scores are indicative of better manual dexterity. We will use this test to determine whether participants improve in their ability to release objects after the synchronously

paired brain and hand stimulation to test Aim 2.

4. Determine conduction time of synchronously pairing the brain and hand stimulation. Determining the conduction time is a common, harmless, minimally discomforting neurophysiological testing procedure performed in many laboratories and clinics world-wide. In order to determine the conduction time, we will electrically stimulate the radial nerve on the dorsal surface of the forearm near the lateral epicondyle (back of the elbow) using the surface Ag-AgCl electrodes and isolated constant current stimulation. We will use Digitimer DS7A system to stimulate the radial nerve. This will give us the conduction time, which tell us how fast the radial nerve is able to transmit information from the back of the elbow to the EDC muscle.
We will use the conduction time to determine the timing of synchronously pairing brain stimulation with functional electrical stimulation (FES)-facilitated motor practice.

We will first collect use-dependent plasticity data followed by motor performance data. Subjects will be provided adequate rest breaks as needed.

The clinical, motor and TMS and assessments will be conducted at the Neuormotor Recovery Rehabilitation lab, which is located in the Keystone building of the University of Pittsburgh. These assessments will be conducted by the personnel trained and supervised by the PI. The MRI scan will be conducted at the Magnetic Resonance Research Center facility of the University of Pittsburgh, which is located in UPMC Presbyterian.

PROCEDURES FOR ADMINISTERING SYNCHRONOUSLY PAIRED BRAIN AND HAND STIMULATION FOR SEVERE STROKE (total participant time: 1 hour each session):

1. Determining reaction time prior to the synchronously paired M1 stimulation with FES facilitated motor practice session: Prior to the practice session, we will determine each participant’s reaction time required to release a spherical object (i.e. a lightweight ball of 10” diameter). We chose a large diameter spherical object because it allows maximum finger extension. The participants will first grasp the object when prompted by the ‘Ready’ visual cue and upon hearing an auditory ‘Go’ cue will extend the wrist and fingers to release the object within their ability. Participants will perform 20 trials. The spherical object is placed on a funnel shaped trough such that the participant’s wrist and fingers can be placed directly on top of the spherical object. The spherical object is attached to the bottom of the trough with weighted strings, which will prevent the object from falling out of the trough. The Intan RHD2000 Recording Controller (IRC, Intan Technologies, Los Angeles, CA) will be used to record the EMG from the EDC muscle.

We will use the onset of EDC activity to determine reaction time. EMG will be rectified and smoothed (rsEMG) with a 10 Hz lowpass filter, and the onset time is defined as the point where the rsEMG increases to 10% peak amplitude.

2.Synchronously paired M1 stimulation with FES-facilitated motor practice session: Participants will be seated in a custom chair with their arms supported by height adjustable arm-rests. A host PC running MATLAB will display instructions and control the timing of events in each trial. An Arduino microcontroller (model Uno) is connected via USB to the PC and generates digital event markers and performs EMG onset detection in real-time. Each trial will begin with a 'Ready' cue, which prompts the participant to prepare and also initiate the start of data acquisition. An audible 'Go' cue (a 750 ms tone) is issued by the Arduino at a variable latency (5-8 s) after the 'Ready' cue. A timer set to the user-specific reaction time (see above) begins counting down at the onset of the 'Go' cue. When the reaction timer reaches zero, the Arduino issues a digital trigger to the TMS system, delivering a TMS pulse (at 70%, 100% or 130% intensity) to the "motor hotspot" either before FES (mean reaction time – 50-75 ms) or with the onset of FES (reaction time – 0 ms). TMS will be delivered with a MagStim 2002 Magnetic Stimulator, figure-eight 70 mm D coil (MagStim Ltd., Wales, UK) using the neuronavigation system (BrainSight, Rogue Research, Montréal, QC). The Arduino will also issue a digital trigger to the DS 7A stimulator (Digitimer, UK), which will deliver FES to the EDC muscle. DS 7A is a stimulator approved by the Food and Drug Administration, which can be used to provide functional electrical stimulation. Based upon previous studies (Cauraugh et al., 2009), we will provide FES according to six standardized settings: (1) 1 second ramp up; (2) 5 seconds of biphasic stimulation at 50 Hz; (3) 15 to 29 mA stimulation range; (4) pulse width of 200 μs; (5) 1 second ramp down; and (6) 25 seconds of rest between trials. The trial ends and data acquisition stops 15 seconds after the "Go" cue. Participants will complete 200 trials of synchronously paired TMS and FES-facilitated motor practice within a session.

Synchronously paired M1 stimulation with FES-facilitated motor practice session duration: Each session will last approximately 1 hour. We will provide adequate rest breaks as needed. The participant can receive a maximum number of 20 sessions with an interval of at least one day between the consecutive session.

STATISTICAL ANALYSIS

Preliminary Analyses: Thorough exploratory data analyses will be conducted to ascertain data characteristics and to screen for outliers. The preliminary exploration of the data will be used to: 1) examine univariate and bivariate distributions; 2) investigate the magnitude of the associations between the dependent variables and the potential covariates (age, gender, time since stroke, stroke severity, upper extremity severity and

affected side); and 3) verify assumptions of the planned primary analyses. Although statistical results will be examined and interpreted, meaningful changes will be recorded as preliminary data to inform larger, more confirmatory projects. We will use an intent to treat approach, whereby all individuals will be retained for analyses, regardless of missing data. Missing data will be examined using available data on subject characteristics. Statistical significance will be set to .05 unless otherwise specified.

Sample size: We will recruit 10 participants to achieve 80% power using a paired *t*-test with an alpha of .05.

Primary Analyses:

Aim: To determine the effect of synchronized stimulation on motor performance and use-dependent plasticity after stroke

We will conduct three separate paired *t*-tests to examine changes in use-dependent plasticity and motor performance before and after the synchronized stimulation intervention. For use-dependent plasticity, we will evaluate percent change in peak-peak amplitude of the motor evoked potentials and for motor performance we will evaluate percent change in the finger extensor muscle fore and number of blocks in the Box and Block Test. Data will be analyzed with an alpha of .05.