Protocol approved: July 16, 2020

Study Title: Transcranial random noise stimulation (t-RNS) After Hand Recovery in Chronic Stroke

Clinical Trials.gov ID: NCT05489146

STUDY PROTOCOL

This is a double-blind pilot randomized control study. Individuals with moderate-to-severe stroke were randomly allocated to two groups:

Screening procedures

After obtaining the informed consent, potential participants were screened in more detail using a medical chart review and standardized clinical assessments.

Participants were recruited through referrals from the UPMC Rehabilitation Institute, UPMC Centers for Rehab Services, and the University of Pittsburgh Stroke Rehabilitation Research Network.

The following procedures were administered to screen potential participants:

1) We reviewed 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.

2) We conducted a brief screen of upper extremity range of motion using a goniometer to determine if individuals are able to actively flex and extend the more-affected shoulder and elbow at least 30°.

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

4) We conducted a brief cognitive screen using Mini Mental Status Examination to screen for cognitive impairments which may confound the results of the study.

5) We also conducted 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.

6) We screened for one side neglect or hemispatial neglect using the Line Bisection Test, which is a quick paper-pencil test.

7) We also screened participants who do not show a motor evoked potential response of the wrist flexor and extensor muscle with the transcranial magnetic stimulation. This is important to determine whether there some pathways from the damaged motor brain areas, which control the movement of the affected hand are intact. This will help to determine the responsiveness of the treatment, because it is futile to give to include and provide intervention to individuals who do not have any pathways (connectivity) intact between the damaged motor brain areas and the affected hand.

DETAILS OF THE SCREENING ASSESSMENTS (total participant time: 1 hour and 30

minutes):

1) Amount scale of Motor Activity Log (MAL):

The Amount scale of the Motor Activity Log measures the amount of use of the more-affected hand during activities of daily living. Items are scored on a 5-point ordinal scale with 0 representing the inability to use the more-affected upper extremity in daily living tasks in the last two weeks and 5 representing as much use of the more-affected hand in the last two weeks as compared to before the stroke. The MAL has been shown to have good reliability and validity.

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2). 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. The VAS has been shown to have good reliability and validity.

3). Modified Ashworth Scale (MAS):

The MAS is a clinical measure of muscle tone and involves the passive movement of the more affected should, elbow, forearm, wrist, and fingers. The MAS has been shown to have good reliability and validity.

4) Mini-Mental State Examination (MMSE):

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

5) Patient Health Questionnaire (PHQ-9):

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

6) Mini-International Neuropsychiatric Interview Hybrid Assessment (MINI):
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.

7) Line Bisection Test (LBT):
Allows screening of patients with hemispatial neglect of the body.

Assessment procedures

All individuals with severe impairments in the weak hand who provided informed consent, completed screening procedures, and meet study criteria will participate in the study. The PI or personnel trained and supervised by the PI will perform the procedures.

Eligible participants were assessed at 3-time points in the study (pre-intervention, post-intervention, and 3 months after completion of treatment). The pre-intervention, post-intervention, 3 months follow-up assessments were conducted at the Neuromotor Recovery and Rehabilitation Laboratory located in the Keystone building of the University of Pittsburgh.

All the pre-intervention, post-intervention, and 3 months follow-up research assessments were videotaped and later reviewed by personnel trained by the PI to re-examine the scores of the assessments.

These assessments were videotaped to monitor assessment procedures and fidelity. After the video recording was completed, the videos will be downloaded to a password-protected (encrypted) hard disk and stored in a locked cabinet in the PI's office. We obscured the faces in the videos to examine facial responses (such as fatigue) to intervention to modify intervention for future sessions.

PRE-INTERVENTION ASSESSMENT: (total participant time: 7 hours)
Descriptive Measures: Medical Record Review: We collected 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. Stroke location and volume were gleaned from neurological images in the medical record. The pre-intervention assessment will be completed over 2 days.

The following assessments were administered:

1) Wolf motor function test (WMFT): to measure functional recovery in the upper extremity

The WMFT is a 15-item test in which participants are given 2 minutes to complete each item. The items increase in difficulty from simple UE movements requiring few degrees of freedom to tasks requiring the coordination of many degrees of freedom of movement. Faster performance is indicative of better UE motor control. The WMFT is a valid and reliable test of UE function post-stroke.

2) Fugl Meyer Upper Extremity Assessment (FMUE): to measure motor recovery in the upper extremity

This scale is considered the gold standard in upper extremity rehabilitation trials and measures motor impairment by asking the participant to perform various arm and hand motions. Items are scored on a 3-point ordinal scale with 0 representing the inability to complete the item and 2 representing the ability to complete the item as asked. The FMUE has been shown to have good reliability and validity.

3) Stroke Impact Scale (SIS): to measure participation in daily life

The Stroke Impact Scale 3.0 (SIS) will be used to measure the impact of stroke on the participant’s health and daily life. The SIS is a stroke-specific health outcome measure. It is a self-report measure and each item is scored on a 5-item Likert scale. We will complete items

from the hand subscale of SIS.

4) Action Research Arm Test (ARAT): to measure arm and hand recovery
The ARAT is a 19-item measure divided into 4 sub-tests (grasp, grip, pinch, and gross arm movement). The test takes 10 minutes to administer and has good reliability and validity.

Performance on each item is rated on a 4-point ordinal scale ranging from:
3: Performs test normally
2: Completes test, but takes abnormally long or has great difficulty
1: Performs test partially
0: Can perform no part of the test

4) Kinematic Measures of the upper extremity (UE) reaching (motion analysis procedures): to measure arm recovery

The data were collected using the Vicon Nexus three-dimensional motion analysis system. The Vicon is a passive infrared video-based motion analysis system. This system is capable of resolving motion in Cartesian space with an error of fewer than .5 millimeters. Calibration was completed both statistically and dynamically prior to each subject evaluation using standardized static and dynamic references. All data were collected and analyzed at 100 Hertz. Fourteen cameras were placed around the participant to obtain multiple views to construct 3D motion.

Participants were seated on a height-adjustable bench with feet flat on the floor. The weak UE was rested, palm down, on a low table placed alongside the weak lower extremity. The UE was in neutral shoulder flexion/extension and rotation and was adducted. Participants reached, pointed to a target, or grasped an object in front of them. Targets were placed at 80% of each participant's arm's length on a height-adjustable table. Participants reached each target five times first with their less-affected UE and then with their weak UE. In addition, participants also performed a table-wiping task for 1 minute. To minimize fatigue, a 1-minute rest break was provided between reaches.

Kinematics of reaches were also videotaped using a digital camera. Adhesive reflective markers (or spheres) were placed on various joints of the upper body including C7 and T10 vertebrae, the acromion process, clavicle, sternum, upper arm, lateral epicondyle of the elbow, forearm, wrist (VICON wrist band), dorsum of the hand, thumb fingertip, index fingertip, and the top of the target. These reflective markers were used to identify all targets and motion vectors of interest.

5) Electroencephalography (EEG) was used to record brain activity. EEG was recorded while the participant is attempting to perform movements of the weak UE, or while they are at rest. EEG uses sensors attached to the scalp (with tape or adhesive) to measure brain activity. We may use audio or visual cues to prompt the movements.

6) Basic Electromyography (EMG) was used to record muscle activity from a few muscles of the forearm. EMG sensors were attached to the forearm (with tape or adhesive) to measure muscle activity.

7) Transcranial magnetic stimulation (TMS) was used to record brain excitability. Participants

were seated comfortably in a chair with armrests in which they can keep their arms and hands in a constantly relaxed position. We placed 9mm Ag/AgCl surface electrodes over the flexor carpii radialis (FCR) and extensor carpii radilias (ECR) muscles. We delivered single pulse TMS using the Magstim system. The TMS coil was placed tangentially to the scalp with the handle pointing posteriorly. The stimulation was applied over the wrist/hand area of the affected motor cortex and individually localized for each participant based on the optimal position for eliciting MEPs. In order to keep the brain target constant throughout the stimulation session, we will use a frameless stereotactic neuronavigation system.

8) H-reflex (spastic reflex) testing was used to record the spastic reflex in the FCR muscle. H-reflex is the reflex reaction of the muscles after electrical stimulation of the peripheral nerves supplying the muscle. Elicitation of the FCR H-reflex itself is a common, harmless, minimally discomforting neurophysiological testing procedure performed in many laboratories and clinics worldwide. In order to elicit the FCR muscle H-reflex, we stimulated the median nerve on the volar surface of the forearm near the medial epicondyle using the surface Ag-AgCl electrodes and isolated constant current stimulation. We used the Digitimer DS7A system to stimulate the median nerve. The Digitimer DS7A system is an FDA-approved system to stimulate peripheral nerves. The response of the median nerve stimulation produces an H-reflex after 25-35 milliseconds, which were recorded by the EMG response from the 9mm Ag/AgCl surface electrodes placed over the FCR muscle. The EMG response from the FCR muscle were used to determine the H-reflex of the FCR muscle. In addition, to normalize EMG values of the FCR muscle, we recorded the M-wave from the EMG electrode of the FCR muscle, which is a response produced at 3-6 milliseconds after the median nerve stimulation. Similarly, in order to normalize the EMG value of the ECR muscle, we recorded the M-wave from the EMG electrode of the ECR muscle. In order to elicit an M-wave response for the ECR muscle, we stimulated the radial nerve on the dorsal surface of the forearm near the lateral epicondyle using the surface Ag-AgCl electrodes and the Digitimer DS7A.

Intervention procedures

Participants were randomized to one of the two intervention groups [transcranial random-noise stimulation (tRNS) and functional electrical stimulation (FES) or FES with sham tRNS] before pre-intervention testing. After randomization, participants underwent pre-intervention testing, followed by intervention 3 times per week for 6 weeks. Participants were enrolled for a total duration of approximately 5 months from pre-intervention to the follow-up phase. The intervention is described in the following paragraphs.

Experimental Group: Transcranial random-noise stimulation and functional training with FES.

The intervention was divided into two procedures:

1). Transcranial random-noise stimulation (tRNS):

The tRNS was applied with the StarStim device from Neuroelectrics Barcelona SL. The StartStim is battery-operated and has 8 channels that can provide low current brain stimulation. The maximum total current the device can output is 2mA (with a current precision of ~1micoA) using a maximum voltage of +/-15V. Participants received low-intensity current, which will not exceed 1.5mA for the first 30 minutes of the intervention while undergoing the 1st block (first 30

minutes) of functional training with FES. The Starstim was programmed such that the Starstim safely shuts off automatically after the first 30 minutes.

We used PiStim electrodes throughout the treatment, which have an area of 3.14 square cm. The Starstim system has a built-in function to adapt the current density to each type of electrode, such that no more than 1.5mA goes to every single electrode. This feature allowed us to safely administer the recommended current intensity throughout the treatment.

We applied electrodes (filled with the conductive gel) to the cleaned sites on the scalp and informed the participants that they might experience a slight tingling sensation during the inspection for scalp impedance. We began the Starstim stimulation protocol after determining that the scalp impedance for each electrode is less than 20 kOhm.

Before delivering the tRNS stimulation for 30 minutes, participants were provided a brief period of stimulation (less than 1 minute) and were asked if they can sustain this stimulation for the next 30 minutes. We immediately terminated the treatment if the participant was not willing to receive the treatment or if the participant reported any adverse events during the treatment.

The Starstim initially gradually ramped up the low-intensity current stimulation for the 1st minute, which is followed by continuous stimulation for the rest of the session.

2). Functional training with FES: Participants performed functional training with FES for one hour, three times a week for 6 weeks during each session of tRNS. Each one-hour session was divided into two-30 minutes blocks of functional training with FES. During the first 15 minutes of the 1st block, Neuromove, an FDA-approved device was used to facilitate wrist and finger flexion (wrist and finger flexor muscles) to practice grasping functional objects by closing the fingers with the Neuromove attached to their weak hand. During the next 15 minutes of the 1st block, the wrist and finger extension (wrist and finger extensor muscles) was facilitated using the same Neuromove device to practice releasing functional objects by opening the fingers with the Neuromove attached to their weak hand.

We repeated the 1st block, which now constituted the 2nd block. Similar to the 1st block, during the first 15 minutes of the 2nd block, we used Neuromove to facilitate wrist and finger flexion (wrist and finger flexor muscles) to practice grasping functional objects by closing the fingers with the Neuromove attached to their more-affected hand. During the next 15 minutes of the 2nd block, the wrist and finger extension (wrist and finger extensor muscles) was facilitated using the same Neuromove device to practice releasing functional objects by opening the fingers with the Neuromove attached to their weak hand.

A list of sample functional tasks is shown below. Participants chose 3 tasks and practice each task for 2 weeks.

Tasks
Reach and Grasp a can/cup, bring to mouth and then release on a surface
Picking and transferring small objects into container
Eating finger foods
Eating with spoon/fork

Picking thin books/note pads and placing them on a shelf
Placing coins
Picking the phone receiver, dialing with the less-affected hand, and placing the receiver.
Placing checkers in a game of connect 4
Opening pill boxes

We provided adequate rest breaks during the treatment if the patients feel tired during the treatment. Participants will only use the FES during research treatment. The Neuromove and the Starstim devices were not given to participants for their in-home use between the investigator's interventions. Participants also completed a tRNS and FES side effects questionnaire immediately after each treatment session.

Control Group: Functional training with FES with sham tRNS
The control group underwent similar functional training with FES but received sham tRNS. Sham tRNS was delivered using the Starstim device. All the procedures of applying the electrodes and checking the impedance were the same for sham stimulation as well. During the stimulation, participants experienced a gradual ramp-up of the low-intensity current stimulation for the 1st minute, which gradually faded away after the 1st minute and participants did not receive any stimulation for the rest of the session.

We provided adequate rest breaks during the treatment if the patients felt tired during the treatment. Participants only used the FES during research treatment. The FES was not given to participants for their in-home use between the investigator's interventions.

All intervention sessions in both the experimental and control groups were videotaped. We randomly examine 15% of sessions in both groups and assess fidelity based on pre-defined principles.

Procedures to prevent interference between the devices:
In addition, all cables from the electrodes of the Starstim device are encased in a small unit that securely attaches to the participant's back of the head. This small unit then wirelessly communicated with the software on the computer. Thus, there were no hanging cables from the Starstim device.
Also, the electrodes of the Neuromove device are directly connected to the Neuromove device and are securely attached to the forearm muscles. Therefore, the two devices are never in direct contact, which will prevent any interference including leakage of current from the portable devices or leads during active treatment.

Procedures to monitor and recognize excessive cortical excitability:
During the treatment: The starstim has an in-built feature, which shuts automatically shuts off if the skin impedance is more than 2 kOhm.
Immediately after treatment: We will ask the participants to complete a tCS side effects questionnaire (attached) to document any side effects and provide adequate treatment if required.

POST-INTERVENTION ASSESSMENT

The assessments, which were administered pre-intervention were administered within one week after the completion of the intervention.

POST-2 (FOLLOW-UP) INTERVENTION ASSESSMENT

We administered the assessments again three months after the completion of the intervention.

STATISTICAL ANALYSIS

Linear mixed model analyses were used to test the added benefits of tRNS on upper-extremity function after stroke. This analysis was performed both for the primary (Fugl Meyer Upper Extremity Assessment) and secondary (grip strength, Wolf Motor Function Test, and hand subscale of stroke impact scale) outcome measures. The participant's group (tRNS, sham-tRNS), time (PRE, POST, POST-2), and group x time interaction were entered as the fixed independent variables along with baseline scores on the respective outcome measures as covariates in the model. Subject was included as a random effect in the model. A significant main or interaction effect was followed by post-hoc analyses using the Sidak multiple comparison procedure. An alpha level of $P<0.05$ was considered significant for all tests.