Contralaterally Controlled FES plus Video Games for Hand Therapy after Stroke

NCT03058796

Study Protocol and Statistical Analysis Plan

Note: The text below was extracted from the IRB protocol for this study, which was first approved on February 9, 2017. The most recent amendment to the protocol was approved on:

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Study Protocol

Abstract

Objectives: This study will determine the effect of integrating two promising therapy modalities for improving upper limb function after stroke, hand therapy video games (HTVG) and contralaterally controlled functional electrical stimulation (CCFES). It is expected that CCFES+HTVG will enhance the motor impairment and functional outcomes achieved by CCFES alone. Secondarily, we will evaluate the effect of baseline impairment and time post-stroke on treatment response, and explore the effects of CCFES+HTVG vs. CCFES alone on cortical activity during a hand task (fMRI assessment).

Research Plan: This is a randomized controlled trial in which stroke patients will be assigned to either CCFES+HTVG or CCFES for 12 weeks. Hand dexterity, upper limb impairment, and upper extremity activity limitation will be evaluated by a blinded assessor at 0 (baseline), 3, 6, 9, 12 (end of treatment), 24, and 36 weeks. Cortical activation will be assessed at 0 and 12 weeks.

Methodology: Up to 52 stroke survivors with chronic (> 6 months) upper extremity hemiplegia will be enrolled and randomized. The two groups will receive equivalent doses of treatment over a 12 week period consisting of 10 sessions per week (7.5 hrs) of self-administered treatment at home plus 2 sessions per week (3 hrs) of group-specific occupational therapy in the lab. The home sessions for the CCFES+HTVG group will consist of CCFES-mediated video game play according to instructions provided during the lab sessions. For the CCFES group, the home sessions will consist of CCFES-mediated hand opening exercise. The lab sessions for both groups will consist of a period of observation and instruction regarding the home sessions followed by CCFES-mediated functional hand task practice.

Clinical Significance: This study will demonstrate the supplemental motor relearning value of virtual reality/video games to CCFES therapy, (2) identify patients most likely to respond to both therapies, and (3) determine whether adding HTVG to CCFES simply enhances cortical activation underlying CCFES or engages additional cortical areas to improve response across broader ranges of severity and chronicity. This study is an important step toward the development and dissemination of new

treatments that may be applicable and effective across a wide range of patients who have lost hand function after stroke.

Specific Aims

AIM 1: Determine the effect of integrating Hand Therapy Video Games (HTVG) with Contralaterally Controlled Functional Electrical Stimulation (CCFES) on upper extremity motor outcomes

Hypothesis 1: Stroke patients treated with CCFES+HTVG will have greater and faster improvements in hand dexterity, upper limb impairment, and activity limitation than those treated with CCFES alone

AIM 2: Evaluate the effect of baseline impairment and time post-stroke on treatment response

Hypothesis 2: Compared to CCFES, CCFES+HTVG will benefit patients with greater baseline impairment and time elapsed post-stroke.

AIM 3: Explore the effects of CCFES+HTVG vs. CCFES on cortical activation during a hand task

Hypothesis 3: Compared to CCFES, CCFES+HTVG will exhibit greater re-mapping in the brain, demonstrated as greater lateralization of activity, greater recruitment of learning- based networks in ipsilesional and contralesional regions, and increased intensity of cortical activity.

Methods and Procedures

General Study Design

A single-blinded randomized controlled trial will be carried out to assess the effects of 12 weeks of CCFES+HTVG compared to CCFES. Dexterity, upper limb impairment, and activity limitation will be assessed at 0 (baseline), 3, 6, 9, 12 (end of treatment), 24, and 36 wks. Cortical activation (measured with fMRI) will be optionally assessed at 0 and 12 wks. The treatment dose will be the same for both groups: 10 sessions per week (7.5 hrs) of self-administered treatment at home plus 2 sessions per week (3 hrs) of group-specific occupational therapy in the lab.

Device

As in our previous CCFES studies,[1-4] this study will use a multi-channel transcutaneous (or surface) stimulator that was designed and manufactured at the Technical Development Laboratory of the Cleveland FES Center. This stimulator is capable of delivering up to 7 independent channels of stimulation (i.e., pulse trains of electrical current), and it can be programmed to send and modulate the stimulation intensity (i.e., pulse width or amplitude) from each channel in response to an analog input signal from an external transducer (in this study, bend sensors attached to a glove). Customized patterns of stimulation are programmed by connecting the stimulator through an isolation module to a desktop or laptop computer. After the stimulator is programmed, it is disconnected from the computer and operates in a free-standing fashion, powered by a rechargeable battery. The programmability of the device allows a researcher to tailor the timing and intensity of stimulation for each subject in order to produce functional hand opening. No surface stimulator exists on the market with this capability and versatility. We have, however, worked with a company (PDI Works, Cleveland, TN) to develop an updated version of our device that performs the same functions but which features a touch-screen programming interface which simplifies the programming process. The new device also could be used in this study. It uses the exact same stimulation pulse circuitry as the original device.

Both stimulators output biphasic symmetric rectangular current pulse trains with pulse parameter ranges that are suitable for surface stimulation. For this study, pulse amplitudes of 40-80 mA, pulse widths of < 250 μs, and pulse frequencies of 35 Hz will be used. Up to 3 channels of stimulation will be used to producing hand opening. Sound and light cues apprise the user of the operational state of the stimulator and prompt the user when to open their gloved hand during exercise sessions. An internal memory stores usage statistics, which can be downloaded to a computer to monitor the subjects' usage of the stimulator. The stimulator is fully programmable through custom and commercially available software (Simulink® from The Mathworks, Natick, MA). A rechargeable lithium ion video camera battery (Sony NP-F570) powers the stimulator.

Stimulation is delivered through standard self-adhering pre-gelled 2"x2" square and 1.25" round electrodes (e.g., PALS®, Axelgaard Manufacturing, Fallbrook, CA). The analog input source for the stimulator is an assembly of three passive bend sensors ¼" wide by 4½ " long (Spectra Symbol, Salt

Lake City, UT) which are either attached by Velcro or inserted through slits cut into the top of the index, middle, and ring fingers of an athletic glove.[3] The sensors act as variable resistors. When the fingers open and close, the electrical impedance of each sensors changes; these impedance changes are supplied as the analog input to the stimulator. The stimulator is programmed to produce current pulses with pulse widths (intensities) that are proportional to input from the glove worn on the nonparetic hand.

The CCFES+HTVG system uses a bend sensor that is worn on a finger of the paretic hand to detect opening and closing. The sensor is attached to a fingerless "glove" and plugs into an analog-to-digital converter module, which in turn plugs into a USB port on a 17-inch touchscreen laptop computer. The computer is an all-in-one unit that requires no other components besides the monitor's touchscreen (no keyboard or mouse) to select and play the games. The computer is configured so that it can only be used for the game play prescribed to the participant and requires a USB key from the investigators to run.

Randomization

Subjects will be assigned to a treatment group using an adaptive randomization algorithm[5] to minimize group imbalances on 4 key patient characteristics: (1) time post-stroke (< 2 yrs vs. ≥ 2 yrs), (2) baseline motor status (moderate vs. severe), (3) paretic side (dominant vs. non-dominant),[6] and (4) fMRI eligibility (yes vs. no). Patients with ≥ 10° active wrist extension, 10° active thumb abduction/extension, and 10° active extension in at least two additional digits will be considered to have "moderate" impairment, and patients with less movement than that who meet all the other motor criteria (see Section 30) will be considered to have "severe" impairment.[7]

Device Set Up

For each participant, a stimulator will be set up to stimulate finger and thumb extension in response to input from the CCFES glove. Up to 3 channels of stimulation will be used. Surface electrodes will be positioned on the forearm to activate the extensor digitorum communis (EDC) and extensor pollicis longus (EPL). Abductor pollicis brevis (AbPB), dorsal interossei (DI), or extensor indicis proprius (EIP) may also be stimulated if they are necessary to achieve functional hand opening. A maximum

stimulation intensity will be determined for each electrode, defined as the pulse width that produces maximum finger or thumb extension without discomfort. These pulse widths will be entered into a program that is then downloaded to the stimulator, ensuring that the stimulator used by each participant is customized to them.

Participant Education

After customizing the stimulator, the treating therapist will instruct and train the participants, and their caregivers if necessary, how to put on the components (i.e., electrodes, glove, and bend sensor for game play if applicable). The electrodes will be outlined on the skin and photographs of the electrodes correctly positioned will assist the subject in placing them correctly at home. An instruction manual will be reviewed with every participant, and each will be trained to operate the stimulator and HTVG (if applicable). The treating therapist will make home visits if needed to troubleshoot any problems the subjects may be having at home.

Study Treatments

The treatment regimens for both groups will last 12 weeks and consist of: a) 10 self-administered sessions per week at home, and b) 20 therapist-guided sessions in the FES Center at the LSCDVAMC (2 per week except on weeks that include an assessment visit).

<u>Self-Administered Home Sessions</u>

The 10 home sessions per week will be distributed so that no more than 2 sessions are done per day (separated by >2 hours), and no more than one session per day on days in which a lab session is scheduled.

For the CCFES group, during each of three 15-min periods, audio cues issued from the stimulator will prompt the subject to attempt to fully open both hands for several seconds, then relax both hands for several seconds, and repeat the cycle. Stimulation will open the paretic hand when the subject opens the contralateral unimpaired hand. The subjects will be instructed to attempt to exert effort to open the paretic hand at the same time they open their non-paretic hand. As in our previous studies, the cue durations will be adjusted every 2 weeks, starting at 6 sec open/14 sec relax (30% duty cycle),

then changing to 8 sec open/12 sec relax (40% duty cycle), and finally 10 sec/10 sec (50% duty cycle). These duty cycles are within the 20% to 50% range of duty cycles used in other NMES studies.[8-12] The purpose of the graded duty cycle is to prevent fatigue early in the intervention and to progressively build greater strength with longer duration muscle contractions.[10] A 3-minute rest will follow each 15-minute period.

For the CCFES+HTVG group, during each of three 15-minute periods, the subject will play one of the 4 previously described games, switching to another game every 15 minutes with a 3-minute break between games. The subjects will use the CCFES system to assist hand opening and will be instructed to exert effort to open the paretic hand at the same time they open their non-paretic hand while playing the games. Because games will be introduced and taught one at a time over the first 4 weeks, during the first two weeks of treatment, the subject will have only learned to play one or two games and therefore will repeat the same game over multiple 15-min periods within a single session. More games will be added (unlocked) as the subject learns them in the lab. The therapist will unlock games and set the difficulty settings for each game at the lab sessions. These settings will be stored on a USB key, which the subject must plug into the home computer in order to play the games at home.

Therapist-Administered Lab Sessions

Lab sessions will last ~1.5 hrs. During the first 20 minutes, the CCFES group will do the repetitive CCFES-mediated hand opening exercise, with the therapist reinforcing instructions to open both hands at the same time in response to the cues. The CCFES+HTVG group will play several minutes of each of the video games they were assigned to do at home, while the therapist adjusts the difficulty levels of the games and/or introduces and teaches a new game. Then, for both groups, for 60 minutes the therapist will instruct and encourage subjects to perform functional tasks with the paretic arm and hand, using CCFES to assist hand opening during task practice. Tasks will involve hand opening and closing to pick up, manipulate, and release objects commonly used in daily life. Task difficulty will progress from easy-to-acquire-and-manipulate to tasks requiring wider hand opening, greater skill, graded hand opening (controlled release), and coordination of hand function with proximal upper limb movement.

Data Collection

Baseline Variables

A clinical coordinator will collect baseline characteristics from the participants' electronic medical record(s) and by interview. Data collected will include demographic (e.g., sex, age, race, pre-morbid hand dominance), stroke-related (e.g., time post-stroke, hemorrhagic or ischemic, cortical or subcortical, right or left, Stroke Impact Scale score), and neurologic data (e.g., side of hemiparesis, cognition, neglect, visual deficits, aphasia), as well as co-morbidities, medications, and cognitive function (Montreal Cognitive Assessment). The balance of these variables between the two groups and their effect on the outcomes will be evaluated.

Adherence

Adherence to the home regimen will be monitored with electronic data logging and participant diaries. The stimulator logs the number of cued hand opening exercise periods completed (CCFES group) and the number of CCFES-mediated hand opening/closing repetitions (both groups). The HTVG system logs game setup/difficulty settings, game performance data (e.g., scores), and number of paretic hand opening/closing repetitions. Participants will also be given a paper diary to log completion of sessions. The diaries will be reconciled with electronic data logs at every lab session, in the presence of the participant to encourage adherence.

Concomitant Therapies

We will enroll only patients who are no longer receiving rehabilitation therapies to the upper limbs. The use of electrical stimulation or other experimental rehabilitation techniques involving the hemiparetic upper limb, changes in spasticity medications, botulinum toxin injections to upper limb muscles, use of an arm sling, and use of a resting hand splint will be discouraged unless it is deemed medically necessary. To account for the potential confounding effect of such concomitant therapies, all concomitant therapies will be documented and any group imbalance will be accounted for in the statistical analysis.

Upper Limb Motor Assessments

All subjects will undergo assessments of hand dexterity (BBT), upper limb impairment (UEFM, Maximum Voluntary Finger and Elbow Extension and Tracking), activity limitation (AMAT) by a blinded assessor at 0 (baseline), 3, 6, 9, 12 (end of treatment), 24, and 36 wks. All assessments will be done with no electrical stimulation. Subjects will refrain from using their stimulators for 24 hours prior to their 3, 6, 9, and 12 week assessments in order to avoid any transient carry-over effect or muscle fatigue.

Box and Blocks Test (primary)

The BBT is a measure of gross manual dexterity, which requires the subject to pick up one block at a time, move it over a partition, and release it in a target area as many times as possible in a 60-sec period.

Upper Extremity Fugl-Meyer Assessment

The UEFM is a measure of post-stroke upper limb motor impairment. The assessor requests the subject to attempt specific volitional movement of the upper limb (shoulder, elbow, forearm, wrist, and hand), and rates their ability to perform each movement using a 3-point ordinal scale (0, cannot perform; 1, perform partially; and 2, perform fully). The maximum score is 66.

Arm Motor Abilities Test

The AMAT assesses the patient's ability to execute specific upper limb ADL tasks and does not allow for compensation with the unimpaired side. The test consists of 9 compound tasks composed of 1 to 3 component tasks performed continuously without the subject's awareness of how the components are defined or scored. Unilateral tasks are performed with the affected upper limb; bilateral tasks are performed using (or attempting to use) the dominant extremity in the same role as prior to the stroke. Each component task is rated on a 0 – 5 ordinal scale: 0, no attempt to use affected limb; 1, attempt to use affected limb but it does not participate functionally; 2, affected limb is used only as a helper or stabilizer; 3, affected limb is used slowly or within synergy patterns; 4, almost normal use of affected limb; 5, normal use. The average score of the component scores is calculated, with the maximum score of 5 possible.

Action Research Arm Test

The ARAT is used to assess specific changes in limb function, assessing a subject's ability to handle objects differing in size, weight and shape. The ARAT is a 19-item test divided into four categories (grasp, grip, pinch, and gross movement). The ARAT more heavily weighted toward measuring reaching abilities (as most of the tasks require reaching), while the AMAT is more weighted toward measuring hand function.

Stroke Upper Limb Capacity Scale

The SULCS is a 10-item test in which stroke patients are rated using a 2-point ordinal scale on their performance of upper limb tasks ranging from reaching forward to manipulating coins. We are interested in assessing the convergent validity of the SULCS and AMAT, so that in future studies we may substitute one for the other.

Maximum Voluntary Finger Extension and Tracking

A custom-built battery powered electrogoniometer that simultaneously records the angles of the finger joints (MP, PIP, and DIP) with Hall-effect sensors will be used.[3] Participants will be seated with their forearm and wrist supported and stabilized in a neutral posture. From this resting posture, they will be prompted by an audio cue to extend their fingers as fully as possible for 4 seconds. This will be repeated three times. The three joint angles will be added together, providing a composite measure of degree of finger extension. The average degree of finger extension attained during the last second of the audio cue will be calculated for each trial and averaged over the three trials. For finger tracking, a sinusoidal trace will scroll across the screen, its peak-to-peak amplitude scaled to the middle 70% of the subject's full active range of motion measured that day. The total degree of finger extension will be displayed as a cursor on the computer screen, and the subject will be asked to trace the track by extending and flexing their finger. Error will be quantified as the average vertical distance between the cursor and the target trace.[3]

Maximum Voluntary Elbow Extension and Tracking

A camera-based optical tracking system (Optotrak®, Northern Digital Inc., Ontario, Canada) will be used. Position tracking LED markers will be mounted to the sternum, shoulder, upper arm, forearm,

and wrist. Digitization of bony landmarks on the thorax, scapula, humerus, and forearm permits transformation of sensor data into local segment coordinates using to a standard protocol. Calculations of elbow angle are made following the recommendations of the International Society of Biomechanics.[13] Participants will be seated with their trunk restrained. In response to an audio cue, they will reach forward from a standardized starting position (i.e., shoulder at 90° abduction, 40° flexion) toward a target positioned directly anterior to the shoulder at a distance just beyond their reach. This will be repeated three times. The degree of elbow extension will be derived from position data. For elbow tracking, the same protocol as used for finger tracking will be followed.[14]

Activity Monitor

Participants will wear accelerometers (ActiGraph, LLC) on both wrists for 3 days prior to and after the treatment phase. Arm use ratio will be computed from accelerometer data, which reflects the duration of paretic arm activity relative to non-paretic activity.[15] Ratios < 1.0 indicate that the paretic arm is active less than the non-paretic arm. Others reported pre-treatment ratios of 0.3–0.5 that can increase to beyond 1.0 after intervention.[15,16] Accelerometry is a method of assessing paretic limb use in the community that has shown high correlation with several clinical measures, including the UEFM.[17]

Subjective Assessments

Stroke Impact Scale

The SIS is a self-report questionnaire that measures changes in function and quality of life in stroke patients. It includes 59 items and assesses 8 domains (strength, hand function, ADL, mobility, communication, emotion, memory and thinking, and participation). The questionnaire will be administered before and after the treatment phase and at 6 months post-treatment.

Fine Motor Skills Related Quality of Life

This questionnaire from the Patient Reported Outcomes Measurement Information System (PROMIS) Neuro-QOL Bank measures change in quality of life related to the ability to perform activities of daily living that require fine motor skills. The questionnaire will be administered before and after the treatment phase and at 6 months post-treatment.

Questionnaires

The WRAT4 (Wide Range Achievement Test 4) will be administered to all non-aphasic Candidates at the baseline visit for use in correlation data analysis. All aphasic Subjects will be administered the PPVT III (Peabody Picture Vocabulary Test) instead of the WRAT4 at baseline (0) weeks of the study at MetroHealth Medical Center for use in correlation data analysis. The WRAT4 is a verbal assessment whereas the PPVT III is a non-verbal assessment. This will allow us to gather baseline cognitive information from both our verbal and non-verbal Candidates. The subjects' impressions of the effectiveness of the intervention, the dose, and the ease of using the device/equipment, and their degree of engagement with the home sessions will be captured with questionnaires. The purpose is to gain insight into how well the device and dosage are tolerated and the subjects' perception of effectiveness. One questionnaire will be administered at all outcomes assessment visits by the blinded assessor and two others at end of treatment by a non-blinded staff member who will have no other interaction with the subjects.

Tower Test (Optional; PI Discretion)

The Tower Test is a well-known test of executive function (Shallice, 1982; Keith-Berg 2002), specifically used to detect deficits in planning. The test consists of a board with pegs and several beads with different colors. The examiner uses the beads and pegs to present the examinee with problem-solving tasks that require the examinee to move beads of different sizes and colors to the three pegs in order to match a series of configurations presented by the examiner. The performance of the examinee is compared to representative samples of individuals of the same age to derive hypotheses about the person's executive cognitive ability. The test would be administered before and after the treatment phase and at 6 months post-treatment.

<u>fMRI Assessment</u>

fMRI Procedure and Equipment

We will utilize blood oxygenation level-dependent (BOLD) fMRI to reveal cortical regions that are active during a motor task performed with each hand in turn. Based on our previous work,[18] we will use a tracking task where patients open and close their fingers to move a cursor up and down to trace a 0.4 Hz sine wave scrolling horizontally across a screen. A mirror mounted to the head coil will allow

subjects to view the tracking task. If necessary, vision will be corrected using lenses inserted into plastic frames. Head movements will be minimized using stabilization pads in the head coil and a bite plate. A bite plate will be created by making a quick dental impression of the subject's teeth. During the tracking task, the bite plate will be place in the subject's mouth and a rod extending from the bite plate will attach it to the head coil. If the bite plate is uncomfortable, it will be removed and the session will be performed without it.

Subjects will be instructed to move all fingers of the designated hand and nothing else to perform the tracking task. Subjects will wear MRI-compatible sensors on both hands that record movement at the finger joints of the index, middle, and ring fingers. Output from the finger sensors of each hand will be summed to provide a composite measure of hand opening/closing. For one set of scans, the peak-to-peak amplitude of the sine wave track will be scaled to oscillate between 15% and 85% of the subject's full active range of motion attainable that day (i.e., the middle 70% of the subject's active range of motion). For subjects who have < 10° of finger movement, the track will be scaled so that it corresponds to an active range of motion of 50° centered at the angle at which the subject's fingers rest. This will allow subjects with no or very little finger movement to see the cursor and give them an opportunity to perform the task. Scaling the track to the subject's attainable range helps keep the participant's effort to do the task uniform from pre- to post-treatment. In a second set of scans, the amplitude of the sinusoidal waveform will be the same at baseline and end-of-treatment: between 15% and 150% of the subject's full active range of motion at baseline. This will allow us to disambiguate any effect of movement extent from that of training-induced changes in finger control.

Subjects will perform the tracking test separately for each hand in a block fMRI design. They will perform 9 blocks of two repeating, alternating conditions, Rest and Tracking, each lasting 45 sec for a total of 6 min 45 sec. For all conditions, the sinewave target will be displayed along with the corresponding prompt, "Rest" or "Track," at the bottom of the screen. For each Track condition the subject will attempt to trace the target with the cursor; for each Rest condition they will watch the screen but execute no finger movements. Investigators will visually monitor for extraneous movements, and any subtle mirror movements in the opposite hand will be detected with sensors. Tracking error will be quantified as the average vertical distance of the cursor from the sinusoidal

target during the Track blocks. Prior to testing, subjects will be allotted five 1-min practice trials in a mock scanner in order to mitigate extraneous movement and head motion, and ensure that non-specific factors as fatigue, understanding of the task, etc. do not affect the fMRI signal.

A Siemens Trio 3T scanner (Siemens, Germany) at the Cleveland Clinic will be used. High-resolution (1 mm^3), T_1-weighted, anatomical images with 176 axial slices and a thickness of 1mm and field of view (FOV) = 256 x 256 mm will be acquired to identify appropriate landmarks and serve as a template upon which functional images would be overlaid. An inversion time/echo (TE) time/repetition (TR) time and flip angle of 1900 msec/1.71 msec/900 msec and 8 degrees will be used. Echo Planar Imaging (EPI) BOLD imaging will be acquired with 160 repetitions of 31-4-mm thick axial slices. Imaging parameters will consist of TE= 29ms, TR= 2.8s, flip angle= 80°, matrix = 128 X 128 and field of view = 256 x 256 mm^2 providing an in-plane resolution of 2 x 2 mm^2.

fMRI Metrics

Activation will be examined in motor cortices bilaterally: primary motor cortex (M1), premotor cortex (PMC), and supplementary motor area (SMA), and in other areas, all of which will be outlined using a standard AFNI atlas as in our previous studies to reduce subjectivity that arises from manually drawing regions around the area of the infarct. For each region, active voxels represent the raw volume of activation or "voxel count". The likelihood of cortical lesions affecting our analysis will be reduced by excluding false positive activation found in infarcted regions. The following indices will be derived to quantify functional re-mapping.

Laterality Index*:* Since our previous work and that of others have found that activation shifts to predominantly ipsilesional motor cortices with significant gains in dexterity, we will study whether the balance of activation between ipsi- vs. contralesional M1, S1 and PMC shifts to the ipsilesional hemisphere with greater recovery.[18-21] Voxel counts will be normalized by comparing *between* the two hemispheres using a laterality index that is calculated as follows.[18,19,22,23] Laterality index = (I – C) / (I + C), where I = the active voxel count in the ipsilesional hemisphere and C = the active voxel count in the contralesional hemisphere. The range of possible values is -1 (entirely contralesional activation) to +1 (entirely ipsilesional activation). Laterality of brain activity during movement of both the paretic

and non-paretic hands will be studied, providing a strong within-subject control. Although the brain activation during non-paretic hand movement cannot be considered "normal", it offers a reasonable method of normalizing and investigating recovery within and across subjects.

Volume and Intensity of Activation*:* Regions in parietal associative, prefrontal and cingulate motor cortices, striatum, and cerebellum may become activated over the course of learning with CCFES+HVTG. Therefore, based on our work and others in fMRI,[20,24,25] we will record volume and intensity of activation of these areas at pre- and post-treatment. The volume, center of mass (avg x, y, z Talairach coordinates),[26,27] and change in BOLD signal intensity (contrast estimate or % increase in β in GLM)[18,28-30] for these regions will be studied. BOLD signal intensity indicates the level of activation of neural networks during performance of a task.[31] We will also identify voxels active at both pre- and post-treatment and note whether intensity increases. Each voxel has a t-statistic value reflecting its difference in intensity from "Rest" to "Track". The average t-statistic value of all voxels in a common cluster will be compared from pre- to post-treatment.[32]

Audio/Visual Recordings

Subjects will be video recorded during the motor outcome assessments to capture a visual documentation of treatment effects. Subjects may be video recorded during the treatment sessions to demonstrate the treatment and outcomes and for scientific and educational presentation purposes.

Selection Criteria

Inclusion criteria:

- > 6 months since a first clinical cortical or subcortical (but not brainstem), hemorrhagic or nonhemorrhagic stroke
- age 21-80 years old
- unilateral upper limb hemiparesis with finger extensor strength of ≤ grade 4/5 on the MRC scale AND a score of ≥1 and ≤ 11/14 on the hand section of the upper extremity Fugl-Meyer Assessment

- adequate active movement of the shoulder and elbow to position the hand in the workspace for table-top task practice (necessary for the lab task practice sessions)
- able to follow 3-stage commands
- able to remember 2 of 3 items after 30 minutes
- surface stimulation of the paretic finger and thumb extensors produces functional hand opening without pain (this will exclude those who have degree of flexor hypertonia that prevents stimulated hand opening)
- Functional passive range of motion (minimal resistance) at elbow, wrist, fingers, and thumb (i.e., there exists enough PROM to reach and acquire table-top objects).
- intact vision and hearing
- medically stable
- full voluntary opening/closing of the contralateral (less affected) hand
- demonstrate ability to follow instructions for operating the stimulator or have a caregiver who will assist them.

Exclusion criteria:

- co-existing neurologic diagnosis of peripheral nerve injury, Parkinson's disease, spinal cord injury, traumatic brain injury, or multiple sclerosis
- uncontrolled seizure disorder
- severely impaired cognition and communication
- uncompensated hemineglect
- arm or forearm skin breakdown or edema (to avoid edema-related shunting of current)
- insensate forearm (to avoid risk of electrical burns)
- history of potentially fatal cardiac arrhythmias
- implanted electronic systems (e.g. pacemaker)
- botulinum toxin injections to any upper extremity muscle within 3 months of enrolling
- pregnant women due to unknown risks of surface NMES during pregnancy
- participating in occupational therapy or other rehabilitation therapies to the upper extremity
- severe shoulder or hand pain

Exclusion criteria related to fMRI procedures include:

- implanted metal devices (e.g., cardiac pacemaker or defibrillator, hemostatic clips, nerve stimulators, insulin pumps, lead wires, cochlear implant, prosthetic heart valve, etc.) or indwelling metal that is incompatible with MRI (e.g., metal splinters in the orbit)
- claustrophobia
- pregnancy

Stroke survivors who do not meet the fMRI-related selection criteria but who do meet the rest of the criteria may still participate in the study, but not the fMRI procedures.

Potential Risks

Skin Irritation – When surface electrodes are used, it is possible that the subject will experience a temporary redness of the skin from either the electrodes, the conductive gel used with them, or any adhesive used to secure them. Skin irritation and redness from the electrical stimulation is also possible, but this possibility is rare and minimized by the type and intensity of stimulation that will be used. Participants will be instructed that redness should fade within an hour and that if redness persists, they should contact study staff. If necessary, electrodes or adhesives will be replaced with an alternative.

Uncomfortable Sensation – Electrical stimulation of a muscle may be perceived as a twitching or vibrating sensation, and may be uncomfortable. Electrical stimulation of a nerve may be perceived as a strong but short shock, and may be uncomfortable. Electrical stimulation of the skin may be perceived as a "pins and needles" sensation and may be uncomfortable. Stimulus parameters will be adjusted to the subject's comfort.

Electrical Hazards – There is a possibility of an electrical shock hazard whenever electrical stimulation is used or whenever electrical equipment is used to make measurements. There is a possibility of an electrical burn whenever electrical stimulation with surface electrodes is used. The equipment to be used has been designed and tested to minimize these risks. Subjects will be trained how to use the stimulator

safely and will be asked to adhere to a list of safety precautions. With these precautions, electrical hazards are rare.

Stimulator Malfunction*:* There is a rare possibility that the stimulator may malfunction and produce painful stimulation after it has been programmed in the laboratory. The sensation may be a sudden burning sensation, which can damage the skin if it does not stop. If participants experience pain from the stimulation, they are instructed to turn off the stimulator, discontinue its use, and contact study personnel.

Fatigue – During the treatment and assessment sessions, participants will practice several motor control tasks repeatedly or will be tested on how well they can move their arm and hand and perform specific tasks. These tasks involve concentration and repetition, and may induce "mental fatigue" from the intensity of concentration required during these tasks or soreness from the repetition. Participants in previous similar studies have reported feeling very tired, needing to nap when they go home, or experiencing headaches following lab sessions. This is similar to what one might experience after working hard in a traditional occupational therapy session. Participants will be given rest breaks as needed during the treatment sessions. Additionally, participants will be encouraged to plan time to rest at home after their lab sessions until they know the effect the sessions will have on them.

Motion Sickness – There is a possibility that the video games could cause motion sickness. Some of the video games feature objects that rotate or move in a way that may cause temporary dizziness or light headedness. This risk is minimized by making the video game animation smooth and by closely matching the subjects' hand movement to what they control in the video game. Some of the video games feature less movement of objects on the screen and may therefore decrease the risk of motion sickness. Subjects will be instructed to stop playing the game if they get motion sickness. Only games that don't induce motion sickness will be used.

MRI Exam – Claustrophobia in the scanner, auditory discomfort due to noise from the magnet, and discomfort if a bite block is used to limit head movement are risks associated with the MRI procedures. Subjects with a known history of claustrophobia will be excluded from this part of the

study. The total amount of time in the scanner per session is expected to be 35 to 50 minutes; the actual scan time per session is expected to be less than 15 minutes. All MRI acquisitions, both anatomical and functional, will be performed within the FDA specified limits of magnetic field strength, gradient flux, and radiofrequency energy deposition. The MRI research scans, therefore, will be of no higher risk than a standard clinical MRI examination.

Breach of Confidentiality – There is a small risk of breach of confidentiality of subject data and protected health information.

Unknown Risks – There may be other risks as yet unknown.

Risk Management

If a subject experiences any of the risks described above, they will be asked to report it as soon as possible to the research team. Skin irritations, electrical burns, and electrical shocks will be assessed and treated by the study physician if necessary. In the event of skin irritations associated with the electrodes, alternative electrodes may be used and/or the use of the stimulator may be temporarily suspended. In the event of uncomfortable sensations associated with the electrical stimulation, the stimulus parameters will be readjusted to the subjects' comfort. In the event of electrical burns, the subject will be retrained in the procedures necessary to guard against their occurrence. In the event of electrical shocks, the equipment will be assessed for faults. All equipment has been designed to minimize the possibility of electrical hazards. All study staff will be informed how to reach appropriate medical personnel should an adverse event occur during treatment or assessment sessions. Participants will be instructed in how to contact study personnel or the appropriate on-call physician should an adverse event occur while at home. There are no known lasting side effects associated with undergoing an MRI examination. Procedures in place for protecting against and minimizing potential risks include the presence of software constraints that limit the maximum deposited RF energy and the maximum magnetic gradient flux. This is a safeguard that is imbedded within the operating system of the MR imager, and will provide the same level of safeguard to the patient in this research study as is present in a conventional clinical MR examination. Therefore, these parameters will be

within the FDA guidelines that have been developed to pose no risk to human subjects. The potential risks are also minimized by careful subject selection, excluding any patient with a contraindication to MRI (e.g. the presence of ferromagnetic metal in body, pacemaker, pregnant) from the pool of eligible subjects, and excluding any patient with a history of claustrophobia to prevent subject anxiety. To further limit any potential for discomfort, time in the scanner will be less than 1 hour. Subjects will wear noise-damping headphones to reduce exposure to MRI noise well below the FDA limit. A microphone in the headphones will allow the subject to communicate with the examiner in an emergency if he/she wants to be removed from the scanner at any time. The risk of maintaining data security will be minimized by keeping data locked in the investigators' offices and by following HIPAA regulations.

In addition to the risk management for the study described above, subjects will be given a group-specific user's manual that describes how to use the stimulator safely. This will be reviewed with each subject before they are sent home with the stimulator. The manual will list the following safety precautions:

SAFETY PRECAUTIONS:

- Avoid handling the electrodes while the stimulator is on. Always remember to turn off the stimulator before you remove the electrodes.
- Place electrodes on the skin only where instructed
- Never position electrodes on the chest, across the heart, or on the neck.
- Do not place electrodes over broken skin as this may cause a skin irritation.
- Do not submerge the stimulator in water.
- Do not use the stimulator in the bathtub or shower
- Do not operate dangerous machinery or drive while using the stimulator.
- Do not sleep while using the stimulator. Remain attentive during use to avoid skin burns.
- Use new electrodes if the reused ones no longer stick to the skin.
- Always wash and dry the skin before applying the electrodes.

- A slight reddening of the skin under the electrode is normal. This should fade after 1 hour once the electrodes are removed. If you notice redness or blistering beyond this, discontinue use and contact study personnel.
- Do not participate in this study if you are pregnant or may be pregnant; the safety of electrical stimulation in pregnancy has not been determined.
- Electrical stimulation should not be used by patients with implanted electronic devices (cardiac demand pacemakers etc.) unless under specialized medical supervision.
- Do not participate in this study if you have a history of potentially fatal cardiac arrhythmias.
- Electrical stimulation should not be used by people who have poorly controlled epilepsy.
- The stimulator has been programmed specifically for the intended user only. Do not let others use the stimulator.

Statistical Analysis Plan

We hypothesize that the CCFES+HTVG group will have greater post-treatment gains than the CCFES group on upper extremity motor outcomes. Exploratory looks at the data will be done before fitting our models. The adaptive randomization should force relatively good balance of potential confounding variables (e.g., fMRI eligible, severity of impairment, time post-stroke), but imbalances in treatment adherence or any other baseline covariate (e.g., lesion location, etc.) or adherence may still require their inclusion as covariates. Each measure will be modeled using a linear mixed effects approach which is well-suited for handling correlated repeated measurements, unbalanced data, and missing data and dropouts in longitudinal studies, while permitting us to control for potential confounders.[1] Least square (LS) means will be calculated using model estimates and adjusted for missing values for each group at each time point. This approach allows comparisons and estimates of treatment group effects at any time point, and also allows comparisons and estimates across time points within groups to evaluate the persistence or decay of the treatment effect. Secondarily, we hypothesized that participants who were less than 2 years after stroke or had moderate hand impairment at baseline would improve more than participants who were more than 2 years after stroke or had severe hand impairment at baseline. A mixed effects modeling analysis will be used similar to the primary analysis to evaluate the effects of time post-stroke and impairment severity. For fMRI data, differences from baseline to EOT in beta coefficient maps for each region of interest will be evaluated with paired t-tests and cluster threshold set to >100 voxels. Between-group comparisons will be made with independent t-tests.