# Stroke Rehabilitation Using BCI Technology

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**RESEARCH PROTOCOL**

**Stroke Rehabilitation Using BCI Technology**

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**Project Summary**

The aim of this study is to determine if functional muscle stimulation, directed by electroencephalogram (EEG) output, can increase the extent of stroke recovery on behavioral measures and induce brain plasticity as measured by functional magnetic resonance imaging (fMRI). Study procedures proposed have been extensively used in our lab for a previously approved study (under approval #2010-0004 and 2015-0439).

**Background and Significance**

Neuroplasticity or Brain plasticity, defined as the brain's ability to acquire new skills and adapt to a new environment, is a fundamental mechanism underlying functional recovery after stroke and other forms of brain injury or with natural ageing (Cramer et al., 2011). Although BCI systems are being increasingly used in studies of motor recovery after stroke, TBI, and other spinal cord injuries, we do not yet understand the brain mechanisms underlying recovery. The motor system constantly adapts to external changes so as to achieve optimum motor performance. Our ongoing study (Young et al., 2014, 2015, 2016; Song et al., 2014, 2015,2016) suggests that noninvasive Electroencephalography(EEG) driven Brain Computer Interface (BCI) systems hold the potential for facilitating recovery in the chronic phase after stroke by synchronizing central or brain activity with peripheral movements and thereby harnessing brain plasticity. These studies confirm that change in the pattern of brain activity that is linked to affected hand movement leads to motor re-learning and induces brain plasticity or reorganization that could lead to improvement in motor function (Ang et al., 2013; Prasad et al., 2010; Shindo et al., 2011). This is of special importance for patients in the chronic phase of recovery that may have little to no spontaneous recovery potential of the affected arm. Given that these patients have also likely exhausted other forms of intervention available to them through proper healthcare channels, it is imperative to explore novel intervention technologies that have shown some promise in this population. In order to be accepted and integrated into regular rehabilitation practice, it is necessary to establish the efficacy of the EEG-BCI approach in a prospective randomized control trial with a larger cohort using well-validated outcome measures. Moreover it is necessary to establish efficacy compared to standard accepted modes of intervention that focus on peripheral or passive movement repetition such as that provided by using functional electrical stimulation of the impaired arm. A recent review and meta-analysis of 18 randomized control trials found that functional electrical stimulation (FES) had a modest effect on activity compared with no intervention or placebo (Meilink et al.,2008). While passive movement repetition can be an effective rehabilitation strategy, the recovery can be slow, painstaking and suboptimal. However few trials have compared the effects of standard FES matched in dose and duration to that provided by novel brain based intervention technologies such as EEG-BCI-FES. Our proposed study will determine the efficacy of active (brain-based or EEG-BCI) FES vs. passive FES in a large size cohort of chronic stroke patients using a prospective randomized well-controlled longitudinal study design and will assess concomitant brain (task fMRI, resting fMRI, and Diffusion Tensor Imaging (DTI)) and behavioral changes in these patients.

**Specific Aims**

- Aim 1: To investigate the efficacy of active FES vs. passive FES, as measured by changes in behavioral measures. Hypothesis: We hypothesize that improvements in motor function will be significantly greater using the active FES therapy than the passive FES therapy.
- Aim 2: To investigate the relationship between brain functional activation patterns and behavior changes induced by active vs. passive FES intervention. Hypothesis: We hypothesize that changes induced by active FES (as measured by brain fMRI and EEG measures) will show greater adaptive brain reorganization changes (i.e. brain changes that correlate with improved outcomes) than that induced by the passive FES.
- Aim 3: To investigate the relationship between brain white matter integrity and behavior changes induced by active vs. passive FES intervention. Hypothesis: We hypothesize that changes induced by active FES (as measured by brain DTI measures) will show greater adaptive brain reorganization changes (i.e. brain changes that correlate with improved outcomes) than that induced by the passive FES.

## Research Design and Methods

This is a prospective, longitudinal study in which stroke patients with upper-limb hemiparesis will be adaptively randomized to two groups: A**ctive FES (aka the experimental group)**, and **Passive FES aka (the control group).** Adaptive randomization in our study will be done based on age and severity of UE impairment (see Figure 1).

**Participants**: 144 patients will be enrolled in the study following inclusion/exclusion criteria below:

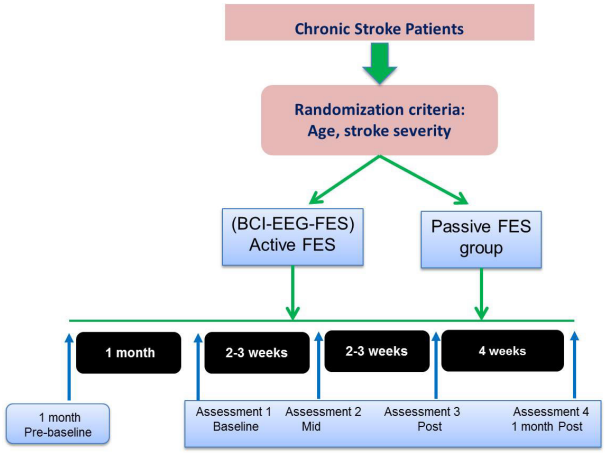


**Figure 1. Schematic of Study Design**

**Inclusion criteria**: ages 50-85 years; new-onset ischemic stroke 12 months prior – chronic time frame; right hand dominant – affected arm; mild to moderate unilateral upper extremity(UE) impairment (Action Research Arm Test; ARAT score > 35) or severe unilateral upper extremity(UE) impairment (ARAT score <= 35); no upper extremity injury or conditions that limited use prior to the stroke; pre-stroke independence with a Modified Rankin Score of 0 or 1, and the ability to provide informed consent on their own behalf.

**Exclusion criteria**: Inability to competently participate in study procedures, Concurrent upper extremity therapy, other neurological (e.g., AD) or psychiatric disorders.

Note, participants with contraindications to MRI will continue to be eligible for this research and will be asked to participate in both the computer training and the behavioral assessments.

**Randomization**: Patients will be adaptively randomized, based on age (50-64 years and 65-85 years), and severity (severe – ARAT > 35, non-severe – ARAT <= 35), to two groups – the active FES group receiving intervention with the active FES (n = 72) and the passive FES group receiving FES only intervention (n=72). Advancing age has a major negative impact on stroke morbidity, mortality; older adults (> 65 years) have increased chance of dying after stroke and being discharged to the skilled nursing facility if they survive, therefore age 65 will be used as a cut-off. There is some evidence that patients with ARAT scores above or below 35 show clear differences in recovery [41], therefore ARAT of 35 will be used as a cutoff.

### Subject identification and Recruitment

Subject Identification:

a) Through referrals by the Stroke Neurology team or other UWHC or UW Rehab hospital or The American Center (TAC) clinicians involved in patient care, in the in-patient or outpatient setting.

b) Clinicians involved in the care of patients may send recruitment letters to eligible patients and ascertain their interest in study participation.

c) A stroke service patient log maintained by the UW-Madison Stroke Neurology section UWHC or UW Rehab hospital or TAC clinicians will be used to identify patients.

d) By posting recruitment flyers in community newsletter, at different locations such as the UWHC, the School of Medicine, UW libraries, the University Station Clinic, St. Mary's hospital, Meriter hospital, as well as UW out-patient clinics and rehab centers outside the Madison area, Madison public libraries, stroke support and other aging support group locations, and on the Principal Investigator, Dr. Prabhakaran's lab

webpage http://radiology.wisc.edu/research/. We will also release ads regarding recruitment in the media – in major newspapers such as the Wisconsin State Journal, the Milwaukee Sentinel, in the Isthmus, and through the Wisconsin Public Radio (WPR).
e) Dr. Prabhakaran, the radiologist involved in clinical imaging protocols of patients, will identify patients who are suitable for study participation as they present to the UWHC, UWMF, WIMR, or Health Emotions Research Institute (HERI) for clinical imaging.
f) We have permission to contact participants who have participated in other stroke research conducted by our group (Prabhakaran 2013-1561, 2015-0469 and 2018-0398). We propose to contact these patients and ascertain interest in participating in this study.

Subject Recruitment:
Dr. Prabhakaran, the radiologist involved in clinical imaging protocols of patients will recruit patients who are suitable for study participation as they present to the UWHC, UWMF, WIMR, or HERI for clinical imaging or patients who contact him in response to the recruitment flyer.

Dr. Justin Sattin, neurologist, and Dr. Kristin Caldera (physiatrist) are involved in the direct care of stroke patients and will aid in participant recruitment.

The study coordinator will be involved in recruiting potential patients referred by Dr. Sattin, Dr. Caldera or their colleagues on the stroke service or patients who contact by telephone or email in response to the recruitment material.

Clinicians involved in the direct care of patients may send recruitment letters to eligible patients and recruit them for the study [recruitment letter attached].

Recruitment flyers and brochures [attached] will be posted in community newspapers and at different locations such as the UWHC, the School of Medicine, UW libraries, the University Station Clinic, St. Mary's hospital, Meriter hospital, Madison public libraries, stroke support and other aging support group locations, nursing facilities (e.g. Oakwood Village, Capital Lakes), Community Centers (e.g. Goodman Community Center), and grocery stores (e.g. Whole Foods, Metcalfe's). Clinicians involved in the direct care of patients may also handout contact cards with the contact information of a study coordinator to potential participants.

Study details will be described to the potential participant by Drs Sattin or Caldera or Prabhakaran. If the patient expresses willingness to participate in the study, his/her name will be forwarded to the research study coordinator for further follow-up, phone screening, and recruitment according to a screening script. Interested patients may also be asked to directly contact the research study coordinator for further information and screening.

Participants responding to the recruitment flyer will be contacting the research coordinator. Potential patients will be screened over phone per a screening script to determine eligibility. A preliminary visit will be arranged so that the patient has an opportunity to visit the facilities and get a tour of the lab as well as ask further questions regarding the study before signing the consent.

During the COVID-19 pandemic, preliminary visits will be stopped and consent procedures will be conducted by phone, when possible, to minimize face-to-face contact subjects have with the research team. A copy of the consent form will be mailed or emailed to subjects prior to the scheduled consent phone call. If emailed, the consent form will be encrypted, if mailed, two copies will be provided. A study team member will call potential subjects at the scheduled time to review the information in the consent form including study procedures, risks associated with participation, alternatives to participation and whom to contact for additional information. Any questions will be addressed during the course of the phone call and

subjects will be encouraged to contact the study team with any questions or concerns they might have at any time. Upon completion of the consent process, a copy of the signed consent form will be provided in one of the following ways depending on each subject preferences and capabilities:

- Electronic signature will be provided using DocuSign
- Subject will be asked to scan a copy of the entire consent document and email it back to the study team.
- Subject will be asked to take a photo of the signature page and email a copy to the study team.
- If subjects are unable to provide an electronic copy of the signed consent form, they will be asked to bring a copy of the form to the research visit.

Prior to the start of any study procedures, all subjects will be reminded that participation is optional and they can change their mind at any time.

All patients that agree to participate will be asked to complete behavioral assessments and optional MRI scans at 5 time points. They will also be required to participate in 15 intervention sessions.

Patients with contraindications to MR will still have the option of being included in this research. They will be asked to complete all but the MR imaging.

**Study Procedures**

A) Behavioral Assessment:

The following commonly used measures of upper extremity motor assessment, standard stroke scales, and measure of activities of daily living will be administered at five timepoints to all patients over the length of the study.

1. The Fugl-Meyer (FM) motor assessment is used to measure voluntary limb movement. It includes the upper extremity (UW0 subscale (33 items; score range 0 – 66) and the lower extremity (LE) subscale (17 items; score range, 0-34) for a total motor FM score of 100.
2. Action Research Arm Test: The Action Research Arm Test (ARAT) is designed for evaluation of upper extremity function. This test consists of sections for Grasp, Grip, Pinch and Gross Movements. Each section is scored separately and the scores added. The maximum possible total score is 57.
3. 9 Hole Peg Test: The 9-HPT is a quick and easy to administer tool for screening fine motor problems in patients. It is a timed test in which nine pegs are inserted and removed from nine holes in the pegboard with each hand.
4. Stroke Impact Scale: The Stroke Impact Scale, or SIS, was created to assess changes in impairments, activities and participation following a stroke will be used in the pre-training and post-training phase of this study. Although the SIS form allows for proxy completion, for this study, participants will be completing the SIS themselves.
5. Barthel Index: The Barthel Index measure a person's daily functioning (activities of daily living and mobility).
6. NIH Stroke scale: The National Institute of Health (NIH) stroke scale (NIHSS) is a standardized method to measure the level of impairment caused by a stroke.
7. Mini-Mental Status Examination (MMSE): The MMSE is a screening tool that provides a brief, objective measure of cognitive function.
8. Center for Epidemiologic Studies-Depression Scale (CES-D): The CES-D is a self-report scale and includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning.

9. EMG(electromyography) – is the recording of changes in skin voltage caused by contraction of the underlying muscles. This recording (EMG) will be obtained using the EMG recording equipment of the BIOPAC systems (http://www.biopac.com/researchApplications.asp?Aid=41&Level=1).
10. Hand grip strength: will be assessed using a dynamometer.
11. Modified Health Questionnaire: to document the general physical health and social habits of all participants.
12. Pain Scale: Patients will be asked to rate their degree of pain on a scale of 0 (no pain) to 5(in tears).[formal instructions for this scale are being included in this addendum]
13. Motor Activity Log: is a structured interview developed to assess the use of the more affected upper extremity (UE) in real-world daily activities.
14. Modified Ashworth Scale –will be used to assess muscle tone.
15. Semantic (category fluency
16. Letter or phonemic fluency (FAS)
17. Trails A and B
18. Span measures – digit span forward and backward (measure of working memory)
19. DSST Mesulam & Weintraub Cancellation task for hemispatial neglect: The Mesulam – Weintraub Cancellation task consists of four test forms utilizing structured and unstructured arrays of verbal and non-verbal stimuli. Subjects are asked to circle all of the targets they can find using different colored pencils so that after every ten targets or a specified time the participant changes pencils so that their search pattern may be identified. The targets are the letter "A" in the verbal and the symbol "☼" in the non-verbal arrays (~ 10 minutes).
20. Depression Screening: For participants 65 and older, we will use the Geriatric Depression Scale - 15 Item. The GDS or the Mood Assessment Scale screens for depression in the elderly. The GDS taps affective and neuropsychological symptoms of depression and consists of 30 yes/no questions. For participants younger than 65, we will use the Center for Epidemiological Studies - Depression Scale. The CES-D is a self-report scale and includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning. The final score spans from 0 to 60, with a higher score indicating greater impairment (~10 minutes).
21. Flanker task: is an executive function/attention task. Subjects are presented with visual stimuli and asked to respond to the direction of a left or right pointing arrow, and ignore flanking arrows that point in the opposite direction as the target arrow.
22. Stroop task: is an executive function/conflict resolution task. In this task the participant tries to name the color of the ink in which a word is printed when the word itself is the name of a color other than that of the ink. Typically, one is slower in this situation than if the color word and the name of the color coincide.
23. Sensory motor computerized task: A computerized task testing participants speed and response time will be developed in-house. The task will require participants to watch the appearance of a target on the left or right of the screen and to click the target as soon as it appears (see Figure 1 http://www.amsciepub.com/doi/pdf/10.2466/05.06.25.PMS.113.4.339-352 for similar approach).
24. Hopkins Verbal Learning Test (HVLT) (Form 1) - The HVLT is a brief test of verbal learning and memory and consists of a list of 12 nouns (targets) with four words drawn from each of three semantic categories. (~ 10 minutes)
25. Montreal Cognitive Assessment (MOCA) – in order to test participant for cognitive impairments [~10 minutes].
26. The Short Blessed Test, a six-item test, used as a diagnostic tool to differentiate patients with cognitive impairments from normal population will be administered. Subjects are asked to answer the items year and month, time of day, count backward 20-1, recite months backwards, and the memory phrase. This test will be administered in addition to the MMSE which also tests for cognitive impairment because the Short Blessed is known to be more sensitive to differences in levels of education and is also quicker to administer. (~ 3-4 minutes)

Pre and post intervention questionnaire – a series of questions to get a sense of the patient's expectations, and general tiredness and motivation levels at the beginning and end of the study, and at the start of intervention each day. The questionnaire administered at the beginning of the study will ask questions regarding any allergies the patient may have and his/her experience with playing computer/video games. The post-intervention questionnaire is to get the patient's feedback regarding their experience in the study.

B) Functional MRI scans

Participants will undergo an MRI scan without contrast lasting approximately 30 - 45 minutes at each of the five study timepoints. Participants' pulse and respiratory rates will also be recorded in the scanner. This will require a pulse monitor (a device comfortably secured to a fingertip that uses light waves to measure pulse and blood oxygen levels) and a respiratory monitor (a belt comfortably secured around the torso that measures the depth and frequency of breaths). Neither monitor confers any risk to participants. fMRI scans will be collected while the participant is performing executed and imagined motor tasks in the scanner to examine corresponding brain activation.

Based on our ongoing study (approved under 2010-0004, 2015-0469), it is our experience that some of these patients will show contraindications for MRI (e.g., have implant or are claustrophobic etc.). We therefore propose to recruit patients who have contraindications for MRI and have them complete the behavioral assessments and intervention components of the study only.

C) Intervention

**Passive FES (the control group):** Functional Electrical Stimulation (FES) of the upper extremity is delivered through a pair of 2" x 2" square electrodes, commercially available stimulus isolator units, which ensure clean, opto-electrical isolation, placed securely on the affected forearm using highly conductive Electrolyte Spray and produced by the LG-7500 Digital Muscle Stimulator (LGMedSupply, Cherry Hill, NJ, USA). The electrodes are placed in half the sessions, superficial to flexor digitorum superficialis to facilitate hand and finger flexion, and in the other half of the sessions superficial to extensor digitorum communis to facilitate hand and finger extension.

Stimulation is controlled through the PC using an Arduino Uno R3 (Adafruit Industries, New York, NY, USA) and a simple reed relay circuit, with the amplitude set to elicit observable muscle activation (e.g. finger grasping) without pain. The pulse rate of the stimulation is set to 60Hz in order to produce tetanic contraction of the muscle and the pulse width is set to 150μs. The input signal will initially be set to zero and adjusted in steps of 5 mA, with allowable stimulation up to 50 mA. All parameters will be adjusted to the patients' comfort level, and testing will be interrupted immediately should a patient report any discomfort.

Training will involve trials of actual or attempted hand movement alternating with periods of rest. Brain activity will be simultaneously recorded using EEG (electroencephalography) technique. EEG electrodes will be attached to the patient's scalp using a standard, commercially available electrode cap.

**Active FES (the experimental group)**: Training will involve trials of actual or attempted hand movement alternating with periods of rest. Patients will be trained to control a cursor on a computer screen using motor-related cortical activity. EEG electrodes will be attached to the patient's scalp using a standard, commercially available electrode cap. We will use the general purpose, freely available BCI computer program "BCI2000" to control signal acquisition, signal processing, and feedback to the participant. The EEG-BCI system will be connected to a FES device and the FES electrodes will be placed on the stroke-affected arm. Electrode placement is similar to that described above for the patients in the passive FES group. The electrodes will be connected to commercially available stimulus isolator units, which ensure clean, opto-electrical isolation. The aim is to elicit motor response in the affected hand in all of the

fingers as evenly as possible. The appropriate level of stimulation that is both comfortable for the participant and sufficiently produces visible movement in the affected hand is estimated and recorded for use in the current and future sessions. All patients will complete 2-3 study visits per week (up to a maximum of 15 sessions) with each session or study visit lasting for about 2 hours.

Study procedures [behavioral visits and intervention] will be photographed and visibly and audibly recorded. Permission will be obtained from the participant before photographs/recording are commenced. The pictures/recordings may be used in the following ways:

- in lab meetings to discuss the participant's progress and possible ways to improve testing
- to assess inter-tester reliability and for training new personnel before they administer the behavioral tests
- in research group presentations with collaborators or at conferences to show examples of participants performing the tasks in this research study

**Compensation for study participation**

All patients will be compensated up to $500 for completing the entire study. Payment of up to $100 ($60 for completing the MRI scan and $40 for completing the behavioral testing) will be provided at the end of each of the five study assessment time-points.

Note since MR scanning is optional, we will offer $60 for each MR scan and $40 for each behavioral assessment/testing session at each visit ($60 for MR scan + $40 for assessment/testing = $100 per visit X 5 = $500).

**Photographs and video recordings** will be completed in such a way that the participant's face will not be identifiable in any future publications of this research.

**Privacy and Confidentiality**

All study procedures are performed in private rooms, by staff that have received HIPAA training and in accordance with clinic practice. Participants may choose not to answer any questions that make them uncomfortable or that they feel violate their privacy. All subject data, including MRI data, will be identified by a participant number. We will take every precaution to protect participant information from a breach of confidentiality with the use of electronic security measures (e.g., passwords). Additionally, paper files will be stored in a locked cabinet when not in use. Participant information will not be disclosed to anyone who is not key personnel on this study without their written permission. To the extent permitted by law, subject identity and participation in this study will remain confidential.

The participant's name, date of birth, gender, date of MRI scan, and MRI screening form will be obtained for the MRI scan log (participant info form). In addition, information from patient medical records such as medications, medical history, physical exam findings, vitals, radiological data, laboratory data, and procedures will also be collected.

The scan logs will be kept in locked cabinets. Only individuals involved with the study will have access to PHI, all identifying information, and all collected datasets which will all be stored in locked cabinets in the PI's Laboratory, study coordinator's office, or on password protected computer systems.

**Data and Safety Monitoring Plan**

Adverse events or problems will be reviewed by the principal investigator as they occur and reported to the IRB in accordance with posted guidelines at http://www.grad.wisc.edu/research/hrpp/hsirbs/hs.AdverseEventAndIncidentReporting.html.

The PI and the co-investigators will meet regularly to review the data and safety monitoring plan to ensure adherence to IRB guidelines.

All researchers and research staff involved in the study have completed Human Subjects and HIPAA training and will be continuously involved in data and safety monitoring. Data and safety monitoring will occur on a continuous basis. fMRI and EEG data will be reviewed by the PI, Co-I and a group of study team members on a continuous basis. All behavioral measures (e.g., ARAT, 9 holepegboard task, SIS etc.) will be reviewed by the study team within a week or two of collection.

**Data Processing/Data Analysis**

For Specific Aim 1:

1a) To investigate the efficacy of active FES vs. passive FES, as measured by changes in behavioral measures. A linear mixed model analysis in SPSS 22.0 will be run for each dependent measure (e.g., ARAT, SIShand function) with Group (active, passive) as the between-participant factor and Time (baseline, mid, post, 1 month post) as the within-participant factor. The two baseline assessments will be averaged so as to get a stable measure of baseline performance prior to receiving intervention.

1b) To investigate the impact of BCI synchronized to FES on behavioral outcomes in the patients in the Active FES group: A post hoc analysis will be done to evaluate whether high-performers of the BCI classification task show more improvement in behavioral measures than low-performers of the BCI classification task. This will allow us to assess to what extent BCI synchronization to FES leads to improved stroke recovery. A median split of high to low performers on the BCI task will be done. We will then compare change in outcome measures of those with high performance on the BCI task (which is synchronized to FES) vs. those with low performance on the BCI task (when there is less synchronization between the BCI and FES) using unpaired t-tests. If there is a difference in the two groups then this is evidence that BCI synchronized to FES contributes to recovery, if there is no difference then this is evidence that BCI irrespective of synchronization to FES contributes to recovery.

For Specific Aim 2: To track fMRI and EEG-BCI based brain reorganization changes and behavioral changes induced by active vs. passive FES. Changes in fMRI and EEG derived LI values over time will be compared in the 2 groups. Group differences in LI at each time-point will be evaluated using Mann-Whitney U test. To determine if there are significant main effects for groups and time, and significant interaction of Group X Time, we will perform Linear Mixed Model analyses. To test if change in fMRI and EEG derived LI, across multiple time-points correlate with change in behavioral measures: The difference in each measure, example from time-point 1(T1) to T2 (i.e. change score, $\Delta$LI) will be calculated and separate correlation (Pearson or Spearman rho) analyses will be performed to see if change in fMRI and EEG significantly correlate with change in behavioral scores ($\Delta$ARAT or $\Delta$SIS-hand function etc).

EEG Data Statistical Analysis: The independent variables are the signed r-squared values and the coherence estimates. At individual participant level the data consists of average estimates per session for condition/movement/screening phase combination sets, and at group level the estimates consist of grand averages over sessions of each individual participant data in the group. Nonparametric statistical tests will be run by calculating Monte-Carlo estimates of the significance probabilities and critical values from the permutation distribution (Oostenveld et al., 2007), followed by correction for multiple comparison using false discovery rate (FDR). Our priori hypotheses regarding expected changes in the r-squared values and coherence as a result of intervention at C3 and C4 sites will be tested using paired t-tests in MATLAB.

For Specific Aim 3: To track DTI based brain reorganization changes and behavioral changes induced by active vs. passive FES. The Pearson r or non-parametric Spearman rank correlation test, as appropriate, will

be used for correlation analyses between DTI and motor outcome measurements. To test whether change in FA and other diffusion values across multiple time-points correlate with change in scores on the ARAT and the SIS: The difference in each measure, example from time-point 1(T1) to T2 (i.e. change score, ΔFA or other diffusion metrics) will be calculated and separate linear regression analyses performed to see if change in diffusion values significantly correlate with change in behavioral scores. Volume of lesion affecting the white matter will be entered as covariate in the regression analysis.

**Sample size considerations:** Our sample size analysis is based on the primary outcome measure ARAT. For observing a minimally clinically significant difference on the ARAT of 6 points with a standard deviation of 12, from pre to post intervention, we would need a sample size of 44 participants per cell (Age By Severity with 2 levels each). This would give us 90% power to detect a significant difference. This leads to an estimated sample size of 44x4 = 176. With 10% additional recruitment to account for data loss due to participant drop-out or poor quality, we propose to recruit a total of N =192 participants in this study.

Given the challenges in recruiting this population (based on our ongoing study – approved under 2010-0004, 2015-0469), we propose to also recruit patients who have contraindications for MRI and allow these patients to complete the behavioral assessments and intervention components of the study.

With the aim of meeting our sample size requirements, and also to recruit a diverse population, we had teamed up with collaborators at Milwaukee, who are also involved in stroke rehab work. Unfortunately, the original PI at Milwaukee has since moved; we have therefore decided to try and meet our goal of 144 at UW Madison and increase our efforts to recruit from the neighboring counties.

**Potential Risks and Benefits**

EEG Recording: The EEG electrodes are passive and only record ongoing physiological activity. Risks related to the EEG recording system include skin irritation, an unpleasant electrode gel smell, and mild discomfort associated with applying, wearing, and removing electrodes on the scalp, face, chest, and hand.

Functional Electrical Stimulation: All stimuli are presented within the participants preferred stimulus intensity range, from sensation threshold to below maximum level without discomfort. The experimental apparatus cannot deliver a dangerous level of electric current unless several, independent, highly unlikely failures occur. Subjects are under supervision at all times during the experiments. If the sensation becomes aversive, the experimenter can quickly turn off the stimulation device, remove the electrodes from the participant's arms, or simply manually turn down the stimulation amplitude. The FES device is battery operated and so there is no chance of a ground fault.

Functional MRI: MRI, a Class II device, is recognized as a Non-Significant Risk (NSR) device by the FDA. All the systems, features, and accessories that will be used in the scanning of participants under this protocol will be operating outside the limits identified by the FDA as "Criteria for Significant Risk Investigations."

Within this context, there are still several potential hazards associated with a typical MRI scan. All participants will be screened using standard clinical exclusionary procedures, and excluded as necessary to minimize risk associated with these hazards. These hazards include the following:

Magnets and Metals: MRI systems are magnetic. They can attract metal objects. Metal in the body, such as pacemakers or metal fragments in the eye, can be moved and metal in the room can fly into the machine.

Pregnancy: While there are no known adverse effects of magnetic fields on fetuses, there is no medical benefit provided by the studies done under this protocol. To be cautious, women who self-report that they may be pregnant or plan to become pregnant during the study period will be excluded from the study.

Claustrophobia: The tube in the MR system where the participant will lie is small and some people react poorly to being in small places. Those who may react poorly will be excluded from the study.

MRI: Aside from the standard risks associated with persons with certain metallic implants discussed above, no known risks of MRI exist. We know of no risks or adverse effects from the magnetic fields or radio waves used in the standard MRI pulse sequences. A small increase in risk may be associated with rapid gradient waveform switching times associated with fast MR imaging. In certain situations, the rapid switching of gradient waveforms has caused peripheral nerve stimulation in participants. Significant nerve stimulation, however, has not occurred as long as the imaging system has been programmed to stay within certain limitations of gradient strength and switching time (dB/dt). There is no reason to believe that risks may be different for the stroke patients to be recruited in this study. The MR scanners currently being used at the UW stay within these guidelines, and any additional pulse sequences which we program in our laboratory will be designed to stay within the current guidelines for dB/dt established by the FDA.

Some additional screening may be required in order to determine whether certain implants or other types of metal are MR compatible. A confirmatory x-ray may be required, for example, subjects that screen positive for having or having had metal in their eyes may be invited to have an orbital x-ray completed to definitively assess whether a MRI poses a risk. The risk of orbital X-ray is minimal. The average effective dose of radiation from this procedure is 0.1 millisieverts or mSv. This exam will be optional for subjects however, if they refuse to have this confirmatory testing, they will not be allowed to participate.

Minimizing risks. Subjects are under supervision at all times during the experiments and will easily be able to communicate any discomfort. The preferred FES stimulus intensity range will be determined by beginning with very low amplitude stimulation and gradually increasing the amplitude until the participant demonstrates a motor response or indicates their maximal comfort amplitude has been reached. Previous testing has shown that the amplitude threshold for motor response occurs well under the amplitude threshold for stimulation discomfort.

***Medical emergencies> We have 2 MD's on call, Drs. Sattin and Prabhakaran, who will be available to respond and attend to any medical emergency during the course of a study session. In addition, we will contact 911 in the event of an emergency.***

**Benefits**

No immediate benefits are expected for subjects involved in the study. There are significant potential scientific benefits in the translation of new imaging technologies from concept to patient care.

**Data and Record Keeping**

The PI will oversee the management of the study dataset. Data Confidentiality will be ensured by allowing only individuals involved with the study to have access to PHI, all identifying information, and all collected datasets which will be stored in locked cabinets in the PI's Laboratory, or on password protected computer systems. Coding and de-identification of datasets have been described under the privacy and confidentiality section. Data collection methods have been described in detail in the study procedures section. Study records will be kept for seven years after study completion at UW-Madison

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