Treating Depression and Enhancing Locomotor Recovery Post-stroke
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Protocol

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Study Title: Treating Depression and Enhancing Locomotor Recovery Post-stroke

TABLE OF CONTENTS

A.SPECIFIC AIMS

Aim 1: Quantify the effects of treatment on post-stroke depression.

Aim 2: Determine if depression influences response to locomotor rehabilitation.

B.BACKGROUND AND SIGNIFICANCE

Depression is the most common neuropsychiatric manifestation following stroke.[1] With a prevalence of ~30%, post-stroke depression (PSD) affects ~2 million stroke survivors in the U.S.[2,3] Pharmacological treatment for PSD is largely ineffective. [4,5] Thus, alternative approaches are needed to effectively treat PSD. PSD also negatively impacts rehabilitation outcomes. [6] Consequently, subjects with PSD are excluded from major trials and there are no established rehabilitation guidelines for these individuals.

In this project, we will assess the effects of aerobic exercise training (AET), repetitive transcranial magnetic stimulation (rTMS) or their combination on depressive severity as well as locomotor function in persons with PSD. Both AET and rTMS are established stand-alone treatments for non-stroke related depression, though neither has been adequately studied post-stroke. Furthermore, substantive research indicates that AET improves post-stroke locomotor function, thus offering a novel approach for treating PSD as well as an established vehicle to study the effects of PSD on response to rehabilitation.

Significance

Post-stroke depression is common and treatment options are inadequate.

Post-stroke depression (PSD) is the most common neuropsychiatric consequence of stroke. Four out of five individuals develop major depressive disorder (MDD) within seven years of stroke onset and point prevalence estimates for PSD are ~30-40%.[3] Thus, more than 2 million individuals with PSD are presently living in the U.S. Current pharmacological treatments for depression in older individuals are generally ineffective (65-75% will not achieve remission) and often come at the cost of significant side effects (e.g. seizure, delirium and falls).[2] Concerns for these effects combined with disagreement about the underlying mechanisms as well as issues related to poly-pharmacy highlight the need for alternative (non-drug) treatments with fewer side effects to successfully alleviate PSD symptoms.

Stroke has profound effects on walking.

With a surviving cohort of nearly 7 million individuals, stroke is the leading cause of long-term disability in the United States. Of the ~795,000 new strokes occurring in the U.S. each year (CDC -

http://www.cdc.gov/nchs/fastats/stroke.htm.), approximately two-thirds of survivors will have some degree of long term disability, [14] and less than half will progress to independent community ambulation. [15] Even among those who do achieve independent ambulation, significant residual deficits persist, with more than 60% of persons post-stroke reporting limitations in mobility related to walking.[16] The prevalence of post-stroke locomotor dysfunction, coupled with the fact that returning to independent ambulation, is the top priority for individuals in the first year post stroke,[17] necessitates development of effective rehabilitation strategies to reduce disability and improve quality of life for the millions of stroke survivors, their families and caregivers.

Individuals with PSD are largely ignored in rehabilitation research and limited data describe the effects of depression on rehabilitation outcomes.

Clinical trials targeting recovery of walking have historically excluded subjects with MDD. [9,18,19,20] As such, there is an absence of data describing how individuals in this large clinical cohort respond to rehabilitation training. Given the prevalence of PSD, specific information regarding how depressive symptoms can be effectively reduced is a critical first step toward optimizing treatment approaches for these individuals. Further, data describing how depression impacts recovery of walking would be extremely valuable to rehabilitation science and the development of treatment would have a major impact on healthcare delivery.

D. RESEARCH DESIGN AND METHODS (including data analysis) The purpose of this project is to determine the impact of AET, rTMS and their combination (AET+rTMS) treatments on post-stroke depressive symptoms and locomotor function so as to guide the development of a future clinical trial. The PI and investigative team have experience performing all of the necessary methodologies in the proposed studies. Specifically, we have extensive experience using left prefrontal rTMS to treat depression; [26-30] implementing treadmill exercise programs in persons post-stroke[18,31,32]; performing neuromechanical assessments of walking;[33-35] applying advanced neuroimaging techniques to clinical populations;[36-38] and performing TMS assessments of cortical excitability. [39-42] A total of 40 depressed post-stroke subjects will be randomly assigned to one of four groups 1) AET; 2) rTMS; 3) combined AET and rTMS (AET+rTMS) or 4) control (sham rTMS) group (n=10 per condition; equally distributed with mild and moderate MDD). Further, an additional 10 non-depressed post-stroke subjects will complete 8 weeks of AET so as to allow us to determine the effects of PSD on response to training (Aim 2). Training (AET, rTMS and AET+rTMS) will take place over an 8-week period, three times per week on non-consecutive days. Measures of depression (QIDS-SR16) as well as self-selected walking speed (SSWS) will be performed each week. Additional measures of locomotor function (walking endurance) will be assessed prior to training (pre), following 4 weeks of training (mid), upon completion of 8 weeks of training (post), allowing determination of the efficacy (and persistence) of training on these outcomes. (Figure 1)

In addition, when possible full neuromechanical assessments of walking on an instrumented treadmill will be performed at the same time points by collecting: (i) kinetics (3- dimensional ground reaction forces and moments), (ii) kinematics and iii) EMG from each leg. A battery of clinical assessments to evaluate degree of function and disability will be performed pre and post-training time point. We will also utilize a combination of voxel-based morphometry (VBM), diffusional tensor imaging (DTI) and transcranial magnetic stimulation (recruitment curves (RCs) and paired associative stimulation (PAS)) to determine the relationship between changes in indices of neuroplasticity and (changes in) locomotor function.

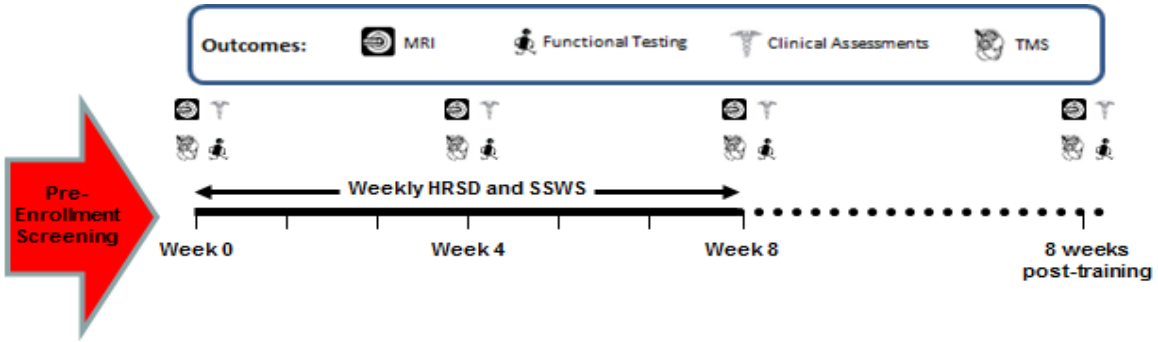

Figure 1: Proposed timeline

Specifically, our outcome measures will be: 1) cortical thickness of the area of M1 associated with the lower extremity via VBM; 2) corticospinal tract (CST) integrity from DTI, reflected by values for fractional anisotropy (FA) and mean diffusivity (MD); 3) excitability of CST circuitry, determined by RCs generated from MEP amplitudes of the medial gastrocnemius and tibialis anterior muscles; and 4) neuroplastic state assessed by PAS. All TMS measurements (but not treatment) will be performed bilaterally and the data used to determine a) the relative contributions of these measures to baseline locomotor function and b) their relationship with individual responses to intervention.

Aim1: Quantify the effects of treatment on post-stroke depression.

Rationale for Aim 1: Both AET and rTMS are effective as stand-alone treatments for non-stroke related MDD. AET is shown to provide benefit for depression both in otherwise healthy individuals,[43,44] as well as in various patient populations. [45-49] Although not specifically studied in persons post-stroke, a study of 338 patients undergoing cardiac rehab showed that two-thirds of depressed patients significantly improved depressive symptoms following AET. [50] Importantly, studies comparing the effectiveness of AET and anti-depressant drugs have demonstrated similar changes in depressive symptoms, and follow-up studies have shown the effects of exercise persist longer than those of antidepressant drugs and exercising subjects achieve higher rates of remission. [51] Repeated left prefrontal TMS (rTMS) is an FDA approved treatment for depression with demonstrated antidepressant effects greater than sham treatment that are both statistically and clinically meaningful in non-stroke related depression. [26,27,29] In addition, rTMS has demonstrated effects in persons with vascular depression (inclusive of stroke) [52] and there is preliminary support for the use of TMS to treat PSD. [53]

Outcome measures for Aim 1: The primary outcome measure we propose is the absolute change in the Quick Inventory of Depressive Symptomatology- Self Report (QIDS-SR16) compared between the four groups. The QIDS-SR16 measures severity of depressive symptoms and is widely used in efficacy studies of antidepressant treatments. Response and remission will be secondary outcomes, with *response* defined as a 50% reduction in baseline symptom severity and *remission* as a QIDS-SR16 score of ≤10. We will conduct weekly QIDS-SR16 each week.

Rationale for Aim 2: Neurological sequelae following stroke produce a multitude of residual functional limitations that contribute to disability and compromised quality of life. Though not yet established in individuals with PSD, substantive research indicates that AET significantly improves post-stroke locomotor function. [7-9] Thus, AET offers an established vehicle to study the effects of PSD on locomotor recovery. In addition, rTMS is a focal, non-systemic and relatively side-effect-free option for treating depressive symptoms that could serve as a powerful and innovative adjunct to stroke rehabilitation. The driving rationale supporting the use of rTMS is that it reduces depressive symptoms, therefore facilitating locomotor recovery by restoring neuroplastic capabilities. Preliminary evidence supports the use of rTMS in treating PSD, [53] as well as plausible mechanisms by which rTMS might augment the effects of AET. We propose to explore the potential synergy of AET and rTMS to determine if adjunctive treatment for depression with TMS improves response to AET.

Outcome measures for Aim 2: Our primary outcome for response to training will be weekly measures of self-selected walking speed (SSWS). Secondary assessments of locomotor function will be the six minute walk test (6MWT). We will also assess changes in brain tissues as indices of neuroplastic changes. Our primary measure of neuroplasticity will be changes in cortical excitability (Recruitment Curve) and neuroplastic state via paired associative stimulation (PAS). Secondarily, we will measure cortical grey matter volume and microstructural integrity (FA and MD via DTI) in the area of the lower extremity motor cortex. We will test if PSD subjects exhibit a reduced neuroplastic state, as demonstrated in the motor cortex in response to PAS stimulation, compared with age (± 5 yrs.) and gender matched non-depressed stroke subjects. PAS is an extremely novel tool to assess neuroplastic state following stroke and has previously been used to demonstrate deficits in depressed (non-stroke) subjects compared with healthy controls.[13,21] Further, decreased cortical grey matter thickness as well as reduced white matter integrity have been correlated with functional performance in persons post-stroke.[55,56]

Treatments:

Repetitive transcranial magnetic stimulation (rTMS) depression treatment: Subjects will undergo repetitive transcranial magnetic stimulation to the left prefrontal region as a treatment approach for depression. [26-30] Treatment will be performed three times per week for eight weeks (24 treatment sessions). A total of 6000 pulses/session will be delivered at 10Hz with an intensity of 120% of motor threshold. All TMS sessions will be overseen by a licensed physician. Although these parameters are greater than the FDA approval in terms of the number of stimuli in a session, we have treated over 100 depressed individuals using this protocol over the past 6 years and the rate of adverse reactions is extremely low (<5%). [58] This dose is well tolerated in non-stroke depressed patients. The FDA approval is for 3000 stimuli, five sessions per week for 4-6 weeks. Given the reduction from 5 sessions/week to 3/week to accommodate the AET schedule, we did not want to under dose and thus increased the number of stimuli in a single session from 3000 to 6000.

Aerobic Exercise Training (AET): Depressed (Aim 1) and non-depressed (Aim 2) subjects participating in AET will complete 24 sessions (3 sessions per week; 40 minutes per session on non-consecutive days). Exercise intensity will initially be set at ~60% of heart rate reserve and progressed throughout the training period. [59] Blood pressure and heart rate will be assessed prior to, during, and at completion of each session so as to determine appropriateness of exercise based on established guidelines. [60] All sessions will be overseen by an exercise physiologist and/or a licensed physical therapist. Overhead harness support will be provided for safety during all training sessions.

Combined rTMS and AET (AET+rTMS) treatment: Subjects receiving AET+rTMS will undergo treatment (3 sessions per week non-consecutive days) for 8 weeks. In these subjects, AET and rTMS treatments will be performed on the same day with the order of treatment alternated from week to week (thus removing the possibility for order effect of delivering the two treatments).

Comparison (control) condition: We will compare treatments (AET, rTMS and AET+rTMS) to a separate control group of subjects in each of the proposed aims (Figure 7). Our comparison group for Aim 1 will be PSD subjects undergoing sham rTMS treatment, similar to the OPT-TMS trial. This will allow us to determine the effects of our active treatments (AET, rTMS or AET+rTMS) on weekly QIDS-SR16 measures while controlling for the regular social interaction and attention from study investigators received in these groups. Sham rTMS has been shown to positively affect depressive symptoms, but to a lesser degree than active rTMS. [26,28-30]

In Aim 2, we will compare the effects of our 3 treatment approaches on locomotor function in depresed subjects to a group of non-depressed subjects undergoing AET. This will allow us to determine if PSD limits response to rehabilitation (AET in depressed subjects vs AET in non-depressed subjects) as well if adjunctive treatment with rTMS improves response to training (AET vs. AET+rTMS).

Quantitative Measures:

Assessment of cortical excitability using TMS: We will use TMS to determine each subject's resting motor threshold (rMT) for both the paretic and non-paretic legs. The rMT is defined as the minimal magnetic pulse resulting in contraction of the target muscle (i.e. medial gastrocnemius or tibialis anterior) as detected by electromyography (EMG) recordings of the motor evoked potentials (MEP). We will also measure the cortical silent period, and recruitment curves to get a full spectrum of analysis of cortical excitability. We will assess this at baseline as well as after 4 and 8 weeks of treatment (or control).

Assessment of cortical excitability and neuroplastic potential via PAS: A means of testing neuroplastic potential, without dependence on subject motivation and effort (frequently impaired in depression) is via a non-invasive brain stimulation protocol called paired associative stimulation (PAS). PAS uses repeated, timed and paired peripheral nerve stimulation and TMS of the contralateral motor cortex and induces consistent changes in excitability of the motor cortex in healthy subjects as demonstrated by changes in the amplitude of MEPs. [61-63] PAS-induced increases in cortical excitability are considered to reflect increased synaptic strength and are at least partially dependent on associative long-term potentiation (LTP) [64,65] which is crucial for neuroplasticity. [66] PAS-induced plasticity is only seen in cortical neurons that receive somatosensory priming, [62] and is likely reliant upon Hebbian mechanisms which are input-specific, timing dependent and associative. These mechanisms are believed to underlie

motor learning [67] hence providing an appropriate model for testing neuroplastic potential. Recent studies have shown that PAS measured neuroplasticity is decreased in depressed patients. [13,21]

We will utilize the PAS measures at baseline, after 4 and 8 weeks of treatment (or control) to assess whether the interventions change PAS measured neuroplastic potential. We will use PAS to assess cortical excitability (difference in pre- vs. post-stimulation MEP amplitude) as well as neuroplastic potential (represented by mean normalized post-stimulation MEP amplitude). We will compare PAS measures at baseline to after either AET, rTMS or AET+rTMS. We will also compare PAS measures in PSD patients to non-depressed post-stroke subjects (Aim 2) to determine whether PSD inhibits neuroplasticity, and if effective treatments reverse the impaired potential for plasticity.

Exercise Tolerance Testing: All subjects will undergo an Exercise Tolerance Test performed according to the protocol used in the recently completed LEAPS trial [68] prior to enrollment. Subjects will perform 3 minute bouts on a cycle ergometer until maximum effort is achieved or the test is terminated for predefined symptomatic, clinical or electrocardiographic criteria. Resting blood pressure and heart rate will be obtained prior to initiation of exercise. During the exercise test, blood pressure readings will be obtained every 3 minutes and heart rate measured continuously from a 12-lead EKG.

Experimental protocol for walking data collections: Overground self-selected and fastest comfortable walking speeds will be measured at the beginning of each session. Treadmill speeds will then be set to match overground speeds for data collections. Subjects will be asked to complete three trials at each speed (~30 second trials) during which kinematic, kinetic and EMG data will be captured. Subjects will be allowed to wear their own shoes and be asked to walk without an assistive device or ankle-foot orthosis (*see **Potential Limitations***). A safety harness will protect the subject in the case of a loss of balance and all sessions will be overseen by a physical therapist.

Measure of neural activation coordination: Neural activation coordination will be assessed as the number of independent co-activation patterns (ICPs) present during steady state walking determined from sixteen channels of EMG (bilaterally from the medial gastrocnemius, soleus, tibialis anterior, rectus femoris, vastus medialis, biceps femoris, semimembranosus, and gluteus medius) similar to our published work. [69]

Experimental protocol for MRI of brain: All subjects will undergo high-resolution MRI in a 3T scanner (TIM Trio, Siemens) equipped with a thirty-two channel head coil. From each subject, two sequences will be obtained. First, a T1-weighted image with 1 mm isotropic voxels will be acquired in the sagittal plane and voxel-based morphometry (VBM) performed to measure cortical grey matter thickness over the lower extremity motor cortex. Second, diffusion-weighted images will be acquired and used to calculate corticospinal tract (CST) axonal integrity. Finally, subjects may undergo an fMRI sequence at rest and with a simple finger tapping activity.

Clinical Assessments: In addition to our clinical measures of locomotor function (e.g. 6MWT, Fugl-Meyer LE subtest), we will perform clinical assessments of balance (DGI and BBS), quality of life measures and questionnaires (SIS, NHIS Falls Questionnaire) as well as additional measures of depressive symptomology (PHQ-9 and Beck Depression Index). These clinical assessments are standard to most post-stroke locomotor rehabilitation trials. Including these assessments strengthens our design by allowing us to make conclusions regarding the effects of our intervention that extend beyond the measures of walking and/or depressive symptoms. We feel that the proposed benefits of our treatment will be most significant if they are shown to impact behaviors other than that which is targeted as the primary outcome and relate to other domains of function suggested to put individuals post-stroke at risk for disability. All the proposed clinical assessments will be performed by a staff physical therapist or trained study staff blinded to information regarding response to training.

Subjects: Subjects (male and female), ages 18-70, will be screened and recruited for the study greater than 6 months following stroke. Diagnosis will preferably be confirmed by a positive CT or MRI performed during stroke admission but image collection and storage will not part of these study procedures. If images are not available, subject self-report with characteristic deficits, or medical documentation will be accepted. **Inclusion criteria** will be: 1) age 18-70, 2) stroke greater than 6 months ago , 3) depressive disorder (PHQ-9 > 5) 4) residual paresis in the lower extremity (Fugl-Meyer LE motor score <34), 5) ability

to walk without assistance and without an AFO on the treadmill ≥ 30 seconds at speeds ranging from 0.2-1.0 m/s, 6) no antidepressant medications or clinically able to discontinue medications, 7) provision of informed consent. In addition, all subjects who meet criteria for the training portion must complete an exercise tolerance test and be cleared for participation by the study cardiologist. **Exclusion criteria** will be: 1) Unable to ambulate at least 150 feet prior to stroke, or experienced intermittent claudication while walking; 2) history of congestive heart failure, unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during ADL's; 3) History of COPD or oxygen dependence; 4) Preexisting neurological disorders, or dementia; 5) History of major head trauma; 6) Legal blindness or severe visual impairment; 7) history of psychosis or other Axis I disorder that is primary; 8) Life expectancy <1 yr.; 9) Severe arthritis or other problems that limit passive ROM; 10) History of DVT or pulmonary embolism within 6 months; 11) Uncontrolled diabetes with recent weight loss, diabetic coma, or frequent insulin reactions; 12) Severe hypertension with systolic >200 mmHg and diastolic >110 mmHg at rest; 13) attempt of suicide in the last 2 years or at suicidal risk; 14) Current enrollment in a clinical trial to enhance motor recovery; 15) Presence of non-MR compatible implants, pregnancy or severe claustrophobia.

Subject screening and clinical assessments: After enrollment, participants will be thoroughly evaluated for functional and cognitive impairments as well as physical performance. Descriptive physical performance testing will include the lower extremity Fugl-Meyer Assessment (FMA-LE), Dynamic Gait Index (DGI), Stroke Impact Scale (SIS), Berg Balance Scale (BBS), and the NHIS Falls Questionnaire. The FMA-LE is a 34-point scale assessing lower extremity function through a progression of items examining more complex movements, speed, and coordination. The SIS is a stroke-specific outcome measure that assesses physical function and other dimensions of health-related quality of life: emotion, communication, memory and thinking, and social role function. The physical functioning domain includes strength, hand function, mobility, and activities of daily living. We will use a three-step motor command item as a primary screen for study eligibility. All clinical assessments will be performed by a licensed physical therapist or trained study staff under the supervision of a licensed physical therapist.

Assessment of post-stroke depression: Subject screening for depression will be performed using the PHQ-9. We will include only subjects with MDD (PHQ-9 ≥ 5). In addition, we will assess depression severity using the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR16) and the Beck Depression Inventory (BDI) if applicable. Initial depression severity will be classified as mild (PHQ-9 score: 5-9)), moderate (PHQ-9 score: 10-14), moderately severe (PHQ-9 score: 15-19), or severe (PHQ-9 score: 20-27). Testing and monitoring of depression symptomatology will use the QIDS-SR16 classifications of: None (0-5), Mild (6-10), Moderate (11-15), Severe (16-20), and Very Severe (21-27).

Potential Problems and Alternative Solutions:

Results show no added benefit of combining AET and rTMS: In the event that there is no added benefit (e.g. same or smaller effect size) of combining AET and rTMS, there are still a number of future study directions that are exciting and innovative. If both AET and rTMS positively affect the proposed outcomes, we will pose questions related to dosing and timing of delivery. For example, what is the impact of performing AET following treatment with rTMS and vice-versa via a cross-over study design? Further, if rTMS proves beneficial in alleviating depressive symptoms but AET does not improve locomotor function, this would also suggest treatment with rTMS prior to enrollment in AET. Given the proven effects of AET in non-depressed post-stroke subjects, this scenario (presumably supported by findings form Aim 2) would suggest depressive symptoms limit response to AET and thus depression might need to be treated prior to performing AET. An additional possibility is that AET is effective in improving locomotor function but rTMS does not improve depression. This set of findings would lead us to perform dosing (e.g. intensity and duration of exercise) studies with AET with the goal of maximizing the effects of AET on locomotor improvements in persons with PSD. The final scenario would be that there is no effect of rTMS on depression, nor an effect of AET on walking. In this case, we would need to explore approaches besides rTMS to treat depression prior to performing AET. Given the known benefits of AET in non-depressed post-stroke subjects, this scenario would suggest PSD blocks response

to AET and depression needs to be treated effectively with approaches other than rTMS prior to performing AET.

Effects of lesion location or size are unknown: Lesion location, lesion size and their combination are broadly considered correlates of motor dysfunction and potential predictors of functional motor recovery post-stroke. [70] Some observations suggest that the relevant contribution of lesion location is its relative position to [71] and degree of overlap with the corticospinal tract.[71] In stark contrast, multiple investigators have found no meaningful association between lesion size, lesion location and functional motor status. [72-74] In addition, lesion laterality is suggested by some to influence depression severity, though observations confirming this premise have been wholly inconsistent. [75,76] These conflicting observations highlight the unresolved issue of identifying appropriate neuroanatomical predictors of depression or functional motor recovery.

Many subjects normally wear ankle-foot orthoses (AFO): The biomechanical outcome measures proposed depend on accurate assessment of muscle function during walking. The consequences of abnormalities in muscle force production need to be understood well without an AFO, which may lead to future specific suggestions with respect to task demands that can be met with an AFO. Anecdotally, we know that most post-stroke individuals can walk without an AFO at home as well as during clinical exams. The presence of the safety harness provides adequate reassurance of safety in the event of loss of balance.

Neuromechanical outcomes may be influenced by changes in speed: Traditional biomechanical variables are influenced by walking speed. As such, the possibility exists that as participants change their functional ability throughout training, these variables will increase (or decrease) simultaneously. To account for the potential influence of changes in walking speed on our biomechanical outcome measures (i.e. joint powers and angles), we will perform assessments at both self-selected and fastest comfortable speeds prior to and following training, with additional conditions at the post-training time point that are performed at speeds matched to those performed during the pre-training assessment.

Statistical Considerations:

A primary goal of this project is to generate statistics that are useful in planning a larger randomized clinical trial. In this preliminary study subjects will be randomized to one of four treatment categories generated from our 2 x 2 factorial design (Figure 8). The factors in this design are AET (yes or no) and rTMS (yes or no). The outcomes (QIDS-SR16 for Aim 1 and SSWS for Aim 2) will be measured longitudinally over an 8-week period (total nine measurements). In this pilot study we will have 10 subjects in each of the four treatment categories. The necessary sample size to detect a large difference of 4.5 units in QIDS-SR16 score at the end of 8 weeks is 8 subjects per group (assuming an Intra-class correlation of 0.3 over time for 8 measurements with a standard deviation of 5 units, [77] at 80% power and 5% significance level). We will enroll 10 subjects per group to allow for subject drop out during treatment. This same sample size will have the same power to detect a difference of 0.12 units in SSWS assuming a standard deviation of 0.135. Statistical analyses will be performed through a longitudinal repeated measures ANOVA (using PROC GLIMMIX in SAS©). Additional covariates (baseline QIDS-SR16 and SSWS, gender, lesion laterality) will be considered in secondary analyses. If missing data occur appropriate missing data methods such as multiple imputations will be applied.

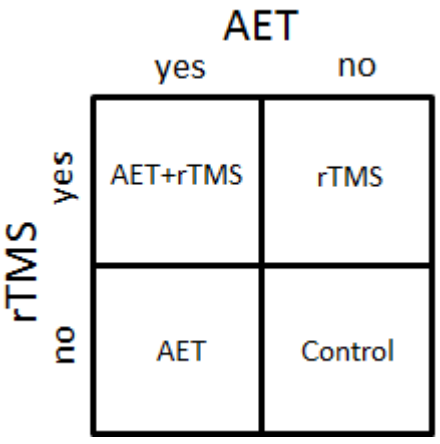

Figure 8: Study design

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics: We plan to recruit up to a total of forty subjects with persistent motoric disability following a stroke, the most recent no less than six months prior. Subjects

may be between 18 and 70 years of age, of either sex, and of diverse ethnic background. Subjects who have experienced more than one stroke will be accepted only if all strokes are on the same side of the brain, there is no history of a clinical ischemic or hemorrhagic event affecting the other hemisphere, and there is no evidence of more than a lacune or minor ischemic demyelination affecting the other hemisphere. Forty depressed post-stroke subjects will be randomly assigned to one of four groups 1) aerobic exercise training (AET); 2) repetitive transcranial magnetic stimulation (rTMS); 3) combined AET and rTMS (AET+rTMS) or 4) control group. All groups with include 10 subjects equally distributed with mild and moderate major depressive disorder (MDD). Subject screening for depression will be performed using the PHQ-9. We will include only subjects with MDD symptomology (PHQ-9 ≥ 5 In addition, we will assess depression severity using the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR16) and the Beck Depression Inventory (BDI) if applicable. Initial depression severity will be classified as mild (PHQ-9 score: 5-9)), moderate (PHQ-9 score: 10-14), moderately severe (PHQ-9 score: 15-19), or severe (PHQ-9 score: 20-27). Testing and monitoring of depression symptomatology will use the QIDS-SR16 classifications of: None (0-5), Mild (6-10), Moderate (11-15), Severe (16-20), and Very Severe (21-27). Further, an additional 10 non-depressed post-stroke subjects (PHQ-9<5) will complete 8 weeks of AET. Training (AET, rTMS and AET+rTMS) will take place over an 8-week period, three times per week on non-consecutive days. Measures of depression as well as self-selected walking speed (SSWS) will be performed each week. Additional measures of locomotor function (walking endurance) will be assessed prior to training (pre), following 4 weeks of training (mid), upon completion of 8 weeks of training (post). In addition, full biomechanical assessments of walking on an instrumented treadmill will be performed at the same time points by collecting: (i) kinetics (3- dimensional ground reaction forces and moments), (ii) kinematics and iii) EMG from each leg. A battery of clinical assessments to evaluate degree of function and disability will be performed pre and post-training. We will also utilize a combination of voxel-based morphometry (VBM), diffusional tensor imaging (DTI) and transcranial magnetic stimulation to determine the relationship between changes in indices of neuroplasticity and (changes in) locomotor function. Specifically, our outcome measures will be: 1) cortical thickness of the area of M1 associated with the lower extremity via VBM; 2) corticospinal tract (CST) integrity from DTI, reflected by values for fractional anisotropy (FA) and mean diffusivity (MD); 3) excitability of CST circuitry, determined by RCs generated from MEP amplitudes of the medial gastrocnemius and tibialis anterior muscles following TMS; and 4) neuroplastic state assessed by paired associative stimulation (PAS). All TMS measurements (but not treatment) will be performed bilaterally and the data used to determine a) the relative contributions of these measures to baseline locomotor function and b) their relationship with individual responses to intervention.

Subjects (male and female), ages 18-70, will be screened and recruited for the study greater than six months post-stroke, allowing for natural recovery during the first 6 months post-stroke. The pool of candidates for the study will be recruited from rehabilitation programs at the Medical University of South Carolina the Clinical Database for Rehabilitation Research in Neurological Conditions (Pro # 00015991), Registry for Stroke Recovery: RESTORE (Pro# 00037803), The Comprehensive Stroke Clinical Biological, Physical and Occupational Therapy Data Repository Pilot Project (Pro# 00020549), Charleston area communities, and word of mouth. Eligible participants will be screened for participation and if appropriate will be accepted into the study for training.

Inclusion criteria will be: 1) age 18-70, 2) stroke greater than 6 months ago, 3) mild-major depressive disorder symptomology (PHQ-9 > 5) 4) residual paresis in the lower extremity (Fugl-Meyer LE motor score <34), 5) ability to walk without assistance and without an AFO on the treadmill ≥ 30 seconds at speeds ranging from 0.2-1.0 m/s, 6) no antidepressant medications or clinically able to discontinue medications, 7) provision of informed consent. In addition, all subjects who meet criteria for the training portion must complete an exercise tolerance test and be cleared for participation by the study cardiologist. **Exclusion criteria** will be: 1) Unable to ambulate at least 150 feet prior to stroke, or experienced intermittent claudication while walking; 2) history of congestive heart failure, unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during ADL's; 3) History of COPD or oxygen dependence; 4) Preexisting neurological disorders, or dementia; 5) History of major head trauma; 6) Legal blindness or severe visual impairment; 7) history of psychosis or other Axis I disorder that is primary; 8) Life expectancy <1 yr.; 9) Severe arthritis or other problems

that limit passive ROM; 10) History of DVT or pulmonary embolism within 6 months; 11) Uncontrolled diabetes with recent weight loss, diabetic coma, or frequent insulin reactions; 12) Severe hypertension with systolic >200 mmHg and diastolic >110 mmHg at rest; 13) attempt of suicide in the last 2 years or at suicidal risk; 14) Current enrollment in a clinical trial to enhance motor recovery; 15) Presence of non-MR compatible implants, pregnancy or severe claustrophobia.

This research will include women and minorities to the extent reflected by composition of the population in Charleston, SC and its surrounding areas. There are no exclusions for sex/gender or race/ethnic group. There will be no involvement of vulnerable populations. At this time, children will not be recruited to be in this study as we are only investigating adults with motor control dysfunction. The targeted enrollment table reflects the 4% of the South Carolina population of Hispanic or Latino descent. There are no collaborating sites at this time.

b. Sources of Materials

All data will be acquired for purposes of research only and will be kept confidential. Data will be coded and not traceable to individuals in any publication. Files will be stored in locked offices or password-protected servers dedicated to Dr. Gregory and key study personnel only.

c. Potential Risks

The risks of the exercise tolerance tests are minimal but could include fainting, falling, irregular heartbeat, and very rarely heart attack, stroke, or death (less than 1 in 2500 cases). Professional staff (exercise physiologist, physical therapist, and cardiologists) will be present and available throughout and emergency treatment will be available if it becomes necessary.

There are no significant risks to the subjects in the proposed AET methods. The risks to individuals participating in this portion of the study are no greater than the risks when providing conventional physical rehabilitation services to an individual after stroke. The same precautions and safety guidelines will be taken that are provided in patient care in rehabilitation settings. The AET program and the clinical testing should not present a risk for the patient but could result in muscle soreness and/or joint stiffness but these symptoms should not persist more than a few days. There is a minimal risk for muscle strains during the testing and training. Under the conditions proposed for this project, MRI is not known to harm living systems. The locomotor assessments used in the proposed study are routine, clinical assessments of gait used in physical therapy clinics and rehabilitation facilities. The GAITRite system has been used to assess walking performance with no adverse reactions or report of discomfort. The experimental protocol to be used in this portion of the proposal involves minimal risk, and is considered standard clinical practice. During all treadmill walking trials, a safety harness will be worn and a physical therapist will be present to provide assistance in the event of loss of balance. The harness will be designed to eliminate the consequences of falling as the device “catches” the subject should they trip or stumble. The presence of this device affords comfort and diminishes the “fear of falling” in subjects.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

A total of fifty subjects (male and female; n=40), ages 18-70, will be screened and recruited for the proposed study. The pool of post-stroke candidates for the study will be recruited from inpatient rehabilitation programs at the Medical University of South Carolina, Charleston, SC, the Clinical Database for Rehabilitation Research (Pro00015991), The Comprehensive Stroke Clinical Biological, Physical and Occupational Therapy Data Repository Pilot Project (Pro00020549) surrounding clinics involved in the care and treatment of stroke survivors, community centers and word of mouth. This study will also recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803), which is a registry with subjects consented for future contact. RESTORE staff will query the registry for potential subjects and provide the Principal Investigator (PI) with the contact information of subjects who meet their criteria. The PI or research staff will contact subject to further screen for potential enrollment. The Stroke Center at the Medical University of South Carolina will assist with recruitment by reviewing the patient rosters to identify potential subjects during inpatient stay. Potential subjects will be given information while inpatient and again when they are seen for follow up in the outpatient clinic for the MUSC Stroke Center. The Stroke

Center research team will establish communication with the potential subjects and act as a liaison with the Principal Investigator to facilitate recruitment. The MUSC Stroke Center sees over 50 new stroke patients per month and routinely screens all patients for eligibility to our various research studies. Subjects will also be recruited utilizing word of mouth. Before any tests are conducted, the protocol and tests to be used in this study and the potential risks and benefits of participation will be explained to each potential subject.

b) Sharing Data
If the subject agrees, the data collected and generated from this study will be shared and linked to RESTORE (Pro# 00037803) and/or to the Clinical Database for Rehabilitation Research in Neurological Conditions (Pro# 00015991) by the subject's registry ID. Sharing data from this study with the registry will allow for more targeted recruitment efforts in the future and allow researchers at MUSC to have a more complete registry with key stroke recovery elements including common data and physical function characteristics that are applicable to multiple studies.

Subjects enrolled in this study also will have the opportunity to participate in Pro00039095 concurrently. For those participants who agree to participate in Pro00039095, data collected and generated from participating in this study will be shared and linked to the data collected in Pro00039095.

c. Protection against Risk

A licensed physical therapist will be present during all AET treatment sessions and a licensed nurse or trained technician will be present for all rTMS sessions. During all treadmill walking trials, a safety harness will be worn to provide assistance in the event of loss of balance. The research staff will closely monitor the subject to ensure their comfort. Any adverse events will be recorded and monitored as required by our Institutional Review Board. In the event of an adverse medical event, standard facility emergency procedures will be followed and proper personnel notified. The PI on this proposal and is a licensed physical therapist with several years of experience in the development and implementation of exercise interventions. Further, Dr. George is a psychiatrist with years of experience using rTMS to treat depression. Any adverse events will be recorded and monitored as required by the IRB. On-site medical services will be available in the event of adverse events to the subjects. Subjects will be able to terminate the training or testing sessions at their request at any time without prejudice. Minimization of risk will be accomplished by monitoring vital signs within prescribed criteria for termination of the AET session. We will follow the American College of Sports Medicine criteria for terminating an inpatient exercise session which includes: subject complaints of light-headedness, confusion, or dyspnea; onset of angina; excessive blood pressure changes (systolic BP greater than 220 mmHg, diastolic BP greater than 110 mmHg); and inappropriate bradycardia (drop in heart rate >10 beats per minute).

Should a participant complete the PHQ-9 and answer questions regarding indicating suicidal thoughts, they will be referred to appropriate medical or mental health professionals. Additionally, should they score above the cut-offs for severe depressive symptoms they will be referred to a healthcare professional. It is outside the scope of this project to diagnose or treat anyone with mental illness. Further action will not be taken unless study participation is affected by course of treatment.

Confidentiality: All records regarding participation in this study will be kept in locked file cabinets in the appropriate laboratories and/or offices, and stored on password-protected computers/servers in the offices and laboratories of the PI's research team. There will be no direct link to participant identifying information (other than subject code) without access to a password-protected computer containing the identifying information linking information to a given subject. Access to linked identifiers is limited to research personnel intimately involved with the human subjects. All data and records acquired from subjects is for research purposes only and will be kept confidential and maintained in a secure database identifiable only by subject code. The results of the study may be published for scientific purposes; however, subjects' identities will not be revealed and data will not be traceable to any individuals in any resultant publications. The information gathered during this study will be kept confidential to the extent permitted by law.

c. Payment to Participants

Participants will receive compensation for participating in this research study based on study related expenses. Reimbursement will be $20/day for each visit and $5/visit for transportation related expenses (e.g. parking, cab or bus fare, metered parking). Total compensation for the study is up to $650 ($520 for participation and $130 for travel related expenses).

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Subjects who participate in this study may see improvements in their own mood or functional ability, but any benefit cannot be guaranteed. Others may benefit from advancement of scientific knowledge. Given the minimal risks involved and the potential for improved functional capacity, the potential benefits of participation make the potential risks reasonable.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

A better and more specific scientific understanding of effects of PSD and its impact on rehabilitation may ultimately lead to a better understanding of neuroplasticity and the extent to which training restores locomotor ability. Given the minimal risks involved and the potential to add to the limited base of scientific knowledge describing this population, the potential risks are reasonable.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

A licensed physical therapist will be present during all treatment sessions. In addition, during all treadmill walking trials, a safety harness will be worn to provide assistance in the event of loss of balance. The research staff will closely monitor the subject to ensure their comfort. Any adverse events will be recorded and monitored as required by our Institutional Review Board. In the event of an adverse medical event, standard facility emergency procedures will be followed and proper personnel notified. The PI on this proposal and is a licensed physical therapist with several years of experience in the development and implementation of exercise interventions. Any adverse events will be recorded and monitored as required by the IRB. On-site medical services will be available in the event of adverse events to the subjects. Subjects will be able to terminate the training or testing sessions at their request at any time without prejudice. Minimization of risk will be accomplished by monitoring vital signs within prescribed criteria for termination of the training session. We will follow the American College of Sports Medicine criteria for terminating an inpatient exercise session which includes: subject complaints of light-headedness, confusion, or dyspnea; onset of angina; excessive blood pressure changes (systolic BP greater than 220 mmHg, diastolic BP greater than 110 mmHg); and inappropriate bradycardia (drop in heart rate >10 beats per minute).

Brain Stimulation Data Safety and Monitoring Plan: We will implement a screening tool for all participants undergoing tDCS that is currently used in the Brain Stimulation Laboratory at MUSC. In addition, Dr. George will personally supervise the first several participants, and Dr. Feng will function as on-site medical supervision for the tDCS trials. Stimulation sessions will be stopped immediately with any complaints of pain or burning at the stimulation sites or for any complaints of dizziness or light-headedness. There are no reported serious adverse events in the literature for tDCS at this time.

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G. CONSULTANTS

n/a

H. FACILITES AVAILABLE

Locomotor Energetics and Assessment Laboratory: This is a 1350 square foot laboratory located within the College of Health Professions Research Building on the campus of Medical University of South Carolina. The laboratory is a shared VA-MUSC resource, is supported in part by the Department of Health Sciences and Research and features equipment capable of collecting kinematic, kinetic, electromyographic, strength, and metabolic data. The motion analysis laboratory is adjacent to a small workshop available for the construction, repair, and alteration of simple mechanical devices.

Locomotor Rehabilitation Laboratory: This laboratory encompasses an 800 square foot space on the second floor of the College of Health Professions research building located on the campus of the Medical University of South Carolina. The laboratory is also a shared VA-MUSC resource and located in the same building as the offices of the center investigators and staff and equipment to facilitate a multi-faceted approach to locomotor recovery after neurological injury. Specialized equipment within the laboratory that is most relevant to the proposed work is a ZeroG mobile body weight support system (only the 6th one installed nationally), a Woodway split-belt treadmill and a Shuttle System lower extremity exercise machine. The focus of this laboratory is on a multi-faceted approach to locomotor recovery after neurological injury, initially targeting stroke and spinal cord injury.

Neuromuscular Assessment Laboratory: This lab is also housed in the College Of Health Professions research building at the Medical University of South Carolina and is designed to investigate the neural and muscular mechanisms underlying abnormal muscle function and the development of effective interventions. Major equipment includes a Biodex System 4 Pro isokinetic dynamometer, GE Logiq ultrasound and a 10 channel EMG system (Motion Lab Systems).

Center for Advanced Imaging Research: The Center for Advanced Imaging Research (CAIR) is a multidisciplinary collaboration of the Departments of Radiology, Neurology and Psychiatry. CAIR's main facility is centered on a new stand-alone imaging research suite, directly across the street from the main hospital as well as the laboratories of the PI, and houses a new Siemens 3T Trio MRI scanner. The scanner operates with a 100% mandate for research use, as delineated in the state-approved certificate of need, and is covered by a master research agreement with Siemens Medical Research. The suite also contains an image analysis laboratory and bioengineering facility along with patient interview and changing rooms. Researchers also have access to other equipment in associated departments, including clinical Siemens 1.5T and 3T Verio MR scanners. A significant component of CAIR is the informatics management system, which consists of an integrated system of Linux workstations surrounding a central core of Linux servers and a growing cluster facility, allowing network access for data retrieval and image analysis both locally and to CAIR members working remotely. A full-time informatics person manages the system, providing system design, trouble-shooting, data export, software maintenance, and systematic backup. Software maintained for CAIR researchers covers a wide range of commonly used contemporary applications for medical image analysis, including SPM, FSL, AFNI, FreeSurfer, Slicer, MedINRIA, MRIcron, Java Image, ImageJ, Camino, jMRUI, and LCModel, as well as a range of more generic analysis tools.

The Brain Stimulation Laboratory (BSL) is located on the 5th floor of the Institute of Psychiatry. BSL studies use electromagnetic approaches as either research tools investigating neuroscience questions or as investigational or FDA approved treatments for brain diseases. Techniques actively being used by BSL researchers and their collaborators include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). The BSL team has been a world leader in TMS research since 1995, performing research studies using TMS as well as using TMS and tDCS in clinical trials.

CLINICAL

MUSC Medical Center: MUSC has a comprehensive range of specialized care centers, including a JCAHO-certified **Stroke Center**. The Stroke Center at MUSC includes highly trained neuroscience nurses, a neuroscience service line administrator, stroke neurologists, neurointensivists, interventional neuroradiologists, diagnostic neuroradiologists, cerebrovascular neurosurgeons, medical intensivists, neurosonology technologists, dedicated neurosciences critical care pharmacists, comprehensive rehabilitation services, dedicated case managers and social workers, and a hospital-based ground transport system. The program holds Joint Commission's *Certificate of Distinction for Primary Stroke Centers which* recognizes centers that make exceptional efforts to foster better outcomes for stroke care. Subjects will be recruited from the inpatient stroke units as well as the outpatient clinic for the MUSC Stroke Center. The Stroke Center research team will assist with recruitment by reviewing the patient rosters to identify potential participants**.** Potential participants will be given information while inpatient and again when they are seen for follow up in the outpatient clinic. The Stroke Center research team will establish communication with the potential participants and act as a liaison with the PI to facilitate recruitment. The MUSC Stroke Center sees over 50 new stroke patients per month and routinely screens all patients for eligibility to our various research studies. In addition to facilitating subject recruitment, these facilities offer the investigators the opportunity to gain exposure to clinical problems by attending grand rounds, observing inpatient rehabilitation, and interacting with clinicians.

I. INVESTIGATOR BROCHURE

n/a

J. APPENDIX

n/a