PROTOCOL TITLE:

Post-Stroke Optimization of Walking using Explosive Resistance: Concurrent effects on Depression (POWER-D Trial)

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

The purpose of this project is to determine the efficacy of POWER training for treating post- stroke depressive symptoms. We will also determine if depression limits response to rehabilitation and the extent to which changes in depression are associated with improvements in functional performance post-stroke. The PI and Co-I's have experience performing all of the proposed methodologies. Specifically, we have extensive experience implementing exercise programs in persons post-stroke; [13,31,32,36] performing assessments of post-stroke walking;[13,36] and diagnosing and treating depression. [37,38,39,40]

Aim 1: Determine the efficacy of POWER training for treating PSD

We hypothesize significant reductions in HRSD scores in both groups, with improvements following POWER greater than control. We also expect greater response and remission rates in the POWER group.

Aim 2: Determine the influence of PSD on the rate and extent of response to POWER training

We posit that POWER training-induced improvements will be attenuated, though still significant, in depressed subjects. In addition, we hypothesize that improvements in walking speed and lower extremity muscle power generation will be contingent upon improvements in HRSD and that a critical threshold will determine the point at which depression is reduced thereby facilitating functional improvements.

2.0 Background

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, approximately two-thirds of survivors will have some degree of long term disability, [18] and less than half will progress to independent community ambulation. [19] 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. [20] Depression contributes directly to disability following stroke and is the single strongest predictor of quality of life. Importantly, improvement in depressive symptoms is associated with better functional recovery and return to activities of daily living. The prevalence of PSD coupled with the fact that returning to independent ambulation is the top priority for individuals in the first year post stroke [21] necessitates development of effective rehabilitation strategies to reduce disability and improve quality of life for the millions of stroke survivors, their families and caregivers.

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 within seven years of stroke onset and point prevalence estimates for PSD are ~30%. [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). [6,22] Importantly, a review of treatment options for PSD found no evidence to support the routine use of drugs or psychological treatments for PSD [5] and in a recent meta-analysis, 23 of 25 prospective studies that met the criteria for inclusion indicated that anti-depressant treatments were a significant predictor of prospective falls, independent of reduced physical

and cognitive function. [23] These issues highlight the need for alternative (non-drug) treatments with fewer side effects to successfully reduce PSD symptoms.

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

Depression is reported to interfere with functional outcomes. [7] Thus, clinical trials targeting recovery of walking have historically excluded depressed subjects. [8,9,10] 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 response to treatment would be extremely valuable to rehabilitation science and the development of effective treatments for PSD would have a major impact on healthcare delivery.

Resistance training can effectively improve post-stroke walking and emerging evidence supports its anti-depressant benefit

Hemiparesis, strictly defined as a muscular weakness or partial paralysis of half of the body, is seen in three- quarters of individuals post-stroke. A primary disability associated with post-stroke hemiparesis is the failure to make rapid graded adjustment of muscle force within the context of purposeful movement patterns, such as are required during walking. Progressive resistance training is widely accepted as the most effective method for developing muscular strength and is currently prescribed by most major health organizations for improving health and fitness. [24] Resistance training improves lower extremity strength following stroke and, when delivered at appropriate intensities, can provide significant functional benefit. [25,26] In contrast, there exist studies in the post-stroke rehabilitation literature that report limited functional benefit of resistance type exercises, some of which fail to elicit significant gains in strength following this type of training. [82,83,84] We recently developed an innovative rehabilitation approach, Post-stroke Optimization of Walking using Explosive Resistance (POWER) training (VA RR&D RX000844). [13,31,32] A unique aspect of POWER training is the focus on high-intensity, high-velocity concentric and eccentric contractions to specifically target post-stroke deficits in muscle power generation. Interventions targeting muscle power (i.e. training at high-velocities) in the aged elicit an over two-fold greater improvement in peak power, when compared to slow velocity training, and explain more of the variability in functional performance. [27,28,29] Data from our trial of POWER training show significant improvements in muscular and locomotor function [13] and a recent pilot study suggest its potential to improve depression (see preliminary studies). The feasibility of resistance training to target depression has been shown in individuals following stroke and data from neurologically healthy subjects suggest the nature of POWER training may be key to its effectiveness for treating PSD. [12] Specifically, trials in older (non-stroke) subjects show benefits of resistance training on depressive symptoms and walking are dependent on training at high intensities, with reduced depression associated with improvements in muscle strength and function. [11] Similarly, high-intensity resistance training significantly improves depression in subjects at high risk for metabolic syndrome, with changes in depression correlated with change in muscle strength. [29]

INNOVATION

Novel approach to treat PSD

The innovative approach proposed herein incorporates an extremely effective therapeutic intervention for post-stroke locomotor function that shows great potential as an anti-depressant treatment, the effectiveness of which could represent a major paradigm shift in post-stroke rehabilitation. Resistance training has shown potential to be an effective stand-alone treatment for non-stroke related depression, the efficacy of which is reportedly similar to antidepressant drugs. [12,13,41] Follow-up studies show the effects of other forms of exercise persist longer and achieve higher rates of remission than pharmacological treatments. Thus, there is a sound rationale to investigate the influence of POWER training on post-stroke depression.

Conceptualizing depression as a state that limits neuroplasticity

Our conceptual framework considers that depression may be associated with disruption of homeostatic mechanisms that regulate neuroplasticity such that rehabilitation may not produce the same brain changes that it does in non-depressed individuals. The concept of impaired neuroplasticity in individuals with PSD is supported by findings of reduced synaptic plasticity in the motor [17] and visual cortices [16] as well as other telencephalic regions such as the hippocampus [30] in depressed patients. Together, these deficits suggest a deficiency in synaptic plasticity that is widespread, and not merely in the limbic and frontal regions that are most closely associated with depression. Although these findings have not been extended to PSD, conceptualizing depression as a disease which fundamentally limits plasticity allows us to pose specific questions regarding how depression limits response to rehabilitation, as well as how effective treatment of depression may improve rehabilitation outcomes. Thus, an extremely exciting possibility is that effective treatment for PSD may result in a virtuous cycle where reducing depression up-regulates neuroplastic responses, thereby facilitating functional gains. That is, effectively treating PSD may actually make an individual better able to recover from stroke.

The work proposed represents the first step in a longer line of investigation aimed at the development of appropriate therapeutic strategies to effectively ameliorate (attenuate) functionally limiting impairments in persons post-stroke. We believe that it will prove impossible to make substantial progress in patient-specific neurorehabilitation evaluation, treatment and outcomes without each being strongly based on a continually refined theoretical framework. Many contemporary neurorehabilitation strategies are based on assumed relationships between impairments of body structure & function, activity and participation; yet little evidence exists to define how these domains mechanistically relate to one another and the personal factors (e.g. depression) that may limit participation. The proposed studies would move this topic forward by elucidating the relationship between changes in depression and functional improvements following training as well as neuroplastic mechanisms of response to POWER training; thereby providing key data for future work to improve the *a priori* identification of fundamental barriers (and facilitators) to therapy.

<u>Preliminary Studies for Aim 1</u>:

POWER training is highly effective at improving post-stroke muscular and locomotor function: (*J Rehab Research & Development.* 52(1):77-84, 2015)

Twelve subjects (6–60 mos. post-stroke) participated in 24 training sessions of POWER training with exercises including leg press, calf raises, and jump training, all performed at high concentric velocity, as well as trials of fast walking. We measured self-selected walking speed as well as knee extensor and plantar flexor strength and power at pre-training, post-training, and at follow-up time points. Post-training improvements in lower

extremity muscle strength and power were accompanied by improvements in self-selected as well as fastest comfortable walking speeds. Specifically, strength increased by 25.0 and 23.3 percent in the paretic and non- paretic plantar flexor (PF) muscle groups, respectively. Improvements in knee extensor (KE) strength were not as large, with gains of 14.8 percent in the paretic side and 16.0 percent in the non-paretic side. Gains in KE peak power of 28.6 and 30.7 percent in the paretic and non-paretic limbs, respectively, were also found post-training. Self-selected walking speed increased from 0.71 to 0.92 m/s, exceeding the clinically meaningful difference reported for participants post-stroke. Fastest comfortable walking speed increased from 1.10 to 1.51 m/s.

POWER training improves depressive severity:

We have enrolled and trained 10 subjects to date with mild to moderate PSD in POWER training. We measured depression severity (HRSD), at pre-, mid- and post-training time points over the 12 week training period. HRSD scores prior to training (15.1 ± 7.5) decreased after 6 weeks (10.8 ± 4.3) and 12 weeks (8.5 ± 3.3) of training. In addition, 7 subjects realized a >50% reduction in depression severity (i.e. response) and 8 were considered to have achieved remission (i.e. HRSD < 10). Although we did not have a comparison group with PSD in this pilot study, these data suggest the potential for POWER training to positively impact depression severity in individuals with PSD.

3.0 Intervention to be studied

Emerging evidence suggests that resistance training is effective at reducing depressive symptoms. [11,12,27] We developed an innovative rehabilitation approach, Post-stroke Optimization of Walking using Explosive Resistance (POWER) training; a high-velocity, high-intensity lower extremity resistance training intervention that improves post-stroke muscular and locomotor function (RR&D RX000844). [13] Preliminary findings from this study suggest POWER training reduces symptoms in those with mild to moderate depression (Figure 1). We seek to build upon these findings to determine its efficacy (vs. control) in treating PSD.

Chronic stroke survivors with mild to moderate depression (n=32) will be randomly assigned to the intervention (POWER) or attention control (stretching) group. POWER training will take place over a 12-week period (3 sessions/week) with exercises including leg press, calf raises, and jump training, all performed at high concentric velocity, as well as trials of fast walking. We will perform bi-weekly measurements of depressive severity using the Hamilton Rating Scale for Depression (HRSD).

Chronic stroke survivors with mild to moderate depression (n=16) as well as age (± 5 yrs), gender and severity-matched (determined by walking speed) non-depressed stroke subjects (n=16) will complete 12 weeks of POWER training. We will perform bi-weekly HRSD measurements as well as comprehensive dynamometric assessments of paretic and non-paretic knee extensor muscle power generation and self-selected walking speed at these same time points. Secondary assessments of locomotor function will be the six-minute walk test (6MWT) and the amount of community walking measured via step activity monitors (SAM).

Stretching is being used as an attention control condition for POWER training. Control subjects will participate in a stretching protocol for the same duration (i.e. 60 minutes per session) and frequency (3 days per week) for 12 weeks to ensure that they have equal interaction with the study staff and controlling for the effects of repeated social interaction on depressive symptoms.

4.0 Study Endpoints

The primary outcome for this trial will be the absolute change in depression using the HRSD from baseline to week 12 compared between AET+rTMS and AET+sham groups.

5.0 Inclusion and Exclusion Criteria/ Study Population

Subjects (male and female), ages 18-85, will be screened and recruited for the study 6-60 months following stroke. The pool of post-stroke candidates for the study will be recruited through the extensive recruiting mechanisms at the local VAMC as well as the Clinical and Translation Tools and Resources CTTR core at MUSC. All participants will have had a new ischemic stroke.

Inclusion criteria will be: 1) age 18-85; 2) stroke at least 6 months prior, 3) residual paresis in the lower extremity (Fugl-Meyer LE motor score <34); 4) ability to walk without assistance and without an AFO during testing and training at speeds ranging from 0.2-0.8 m/s; 5) no antidepressant medications or no change in doses of psychotropic medication for at least 4 weeks prior to the study (6 weeks if newly initiated medication); 6) HRSD question #9 regarding suicide <2; and 7) provision of informed consent. In addition, depressed subjects will screen for probable major depressive disorder (PHQ-9 > 10) and be diagnosed using the Structured Clinical Interview for Depression (SCID) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). All subjects who meet criteria for training must complete an exercise tolerance test and be cleared for participation by the study physician.

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, dementia or previous stroke; 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 assessed by SCID interview; 14) History of seizures or currently prescribed anti-seizure medications; 15) Current enrollment in a clinical trial to enhance motor recovery; 16) Pregnancy verified by urine pregnancy test.

6.0 Number of Subjects

A total of 48 chronic stroke survivors will be accrued locally.

7.0 Setting

Locomotor Energetics and Assessment Laboratory: This 1350 ft^2 laboratory is a shared resource supported in part by the Department of Health Sciences and Research, and features equipment capable of collecting kinematic, kinetic, electromyographic data during walking. This 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 ft^2 space and is also a shared resource. Specialized equipment within the laboratory that is most relevant to the proposed work is a ZeroG mobile body weight support system as well as a Woodway

split-belt treadmill. The focus of this laboratory is on a multi-faceted approach to locomotor recovery after neurological injury, initially targeting stroke.

8.0 Recruitment Methods

Subject recruitment: The pool of candidates for the study will be recruited from rehabilitation programs at the Medical University of South Carolina; the Ralph H. Johnson VAMC; and Charleston area communities. The combination of MUSC Stroke Center and the Ralph H. Johnson provide a unique environment from which to recruit participants for this study and we have on-going collaborative relationships with both entities. The MUSC 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. The Stroke Center research team will assist with recruitment by reviewing patient rosters and potential participants will be given information while inpatient and again when they are seen for follow up in the outpatient clinic. Rack cards and flyers with basic study information and study investigator contact information will be put on display in the MUSC CHP Research Center. Additionally, the rack cards and flyers with be distributed to area rehabilitation clinics.

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, since the proposed research investigates stroke recovery it will be supported by the Clinical and Translation Tools and Resources (CTTR) Core of the NIH-funded Center of Biomedical Research Excellence (COBRE) in Stroke Recovery at MUSC. The CTTR Core provides subject recruitment resources through a bioinformatics-enabled database registry. Currently (November, 2017) there are 663 post-stroke subjects in our database registry and ongoing recruitment is expected to add 1-3 more subjects each week. Of these, 157 have screened positive for PSD (PHQ-9 > 10), all of whom have agreed to be contacted for participation in research studies. As evidence of our ability to recruit subjects with PSD, we (Dr. Gregory and Dr. George) have been successfully recruiting subjects for a trial as part of the South Carolina Center for Stroke Recovery Research. Over the duration of this study (~26 months) we have successfully enrolled subjects with PSD at a rate that would meet the goals for the proposed study. Thus, we are confident that recruitment goals will be met without difficulty.

9.0 Consent Process

Informed consent will be obtained from participants prior to participation. Participants will first be informed of the purpose of the experiments and possible risks. A member of the study staff with then review the Informed Consent form with the potential participant, ensuring they are given adequate time to review the document. The potential participant will be asked if they have any questions about the study, and asked if they agree to participate. The Informed Consent and HIPAA forms will be signed by the participant. Copies of the signed forms will be given to the participant. The consent process will take place in a private room in the MUSC College of Health Professions Building. There will be no set period between informing the prospective participant and obtaining the consent. In every session, participants will be reminded that they may end their participation in the study at any point.

10.0 Study Design / Methods

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), Stroke Impact Scale (SIS), Berg Balance Scale (BBS) and the NIH Stroke Scale**.** 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. [71,72,73] The NIH Stroke Scale measures stroke related impairments including level of consciousness, ability to respond to questions, ability to follow simple commands, deviation of gaze, hemianopsia, facial palsy, limb movements, limb ataxia, sensory loss, neglect, dysarthria, and aphasia. In addition, the Folstein Mini-Mental Status will be used as a screen of cognitive function. Specifically, we will use the three-step command item as a primary screen for study eligibility. All screening and clinical assessments will be performed by a staff physical therapist within the Center for Rehabilitation Research in Neurological Conditions who will be blinded to training group assignment.

Clinical Assessments: The proposed assessments are standard to post-stroke intervention trials. Including these assessments strengthens our design by allowing us to make conclusions regarding the effects of our intervention that extend beyond the behavioral measures of walking. We feel that the proposed benefits of our training 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.

- Dynamic Gait Index (DGI): The DGI evaluates the ability to adapt to changes in task demands. The DGI rates performance from 0 (poor) to 3 (excellent) on eight different gait tasks, including even surfaces, changing speeds, head turns in a vertical or horizontal direction, stepping over or around obstacles, and gait with pivot turns, and steps. [42] The DGI examines complex walking tasks (e.g. accelerating, turning, head turns) and provides valuable information regarding dynamic balance (as opposed to static balance assessed using the BBS) and often reveals deficits that otherwise would not be identified.

- Step Activity Monitor (SAM): The SAM is worn on the ankle to quantify daily step activity. The SAM is a microprocessor-driven accelerometer that permits the researcher to count strides and observe activity during predetermined time spans. The SAM is 98%-99% accurate and has a test-retest reliability post-stroke of 0.98. [43] The SAM will be worn for two consecutive days at a 6-second epoch, per the LEAPS protocol. [8] Information about the effects of POWER training on the amount of community stepping are critical as we attempt to generalize any improvements beyond the laboratory.

- 6-Minute Walk Test (6MWT)**:** Timed walking tests are primarily a measure of functional capacity.[44] The 6MWT tests populations who present with little functional walking capacity and has been validated against the Rivermead Mobility Index (r=0.75) and 10-meter walk time (r=-0.61). [46] The 6MWT has a high intra- and interrater reliability (ICCs = 0.82-0.95). [45]

Assessment of depression severity: The Hamilton Rating Scale for Depression (HRSD) and the Montgomery- Åsberg Depression Rating Scale (MADRS) are the most widely used instruments for obtaining ratings of depressive symptoms. The HRSD samples a broader array of symptoms and is the primary outcome for this project. However, the MADRS is also sensitive to therapeutic change and includes more focus on vegetative symptoms. Thus, we will utilize a single structured interview that contains the questions necessary to complete both the HRSD and MADRS. The order of questions results in a more efficient interview, clustering material of similar content, thereby reducing repetition. Items that require patient observation (e.g., retardation, agitation) or spontaneous patient report (e.g., HRSD mood item) occur towards the end so scores are not contaminated by direct questioning on these topics. Items dealing with somatic symptoms (e.g., sleep) occur before items focusing on psychological state (e.g., guilt, suicide) so as to develop rapport during the earlier part of the interview leading to fuller disclosure of symptoms that are difficult to discuss. Critically, the rater administering the interviews will not be involved with any other aspects of the study. A trained psychiatry practitioner (Dr. George or one of his colleagues) will assess depression severity bi-weekly. Test-retest reliability for the HRSD is extremely high (0.94; 95% CI 0.89-0.97) and thus appropriate to use for repeated measure of depression severity. [41] Depression will be classified as mild (HRSD = 12-16) or moderate (HRSD ≥17) and diagnosed upon enrollment using the Structured Clinical Interview for Depression (SCID) according to the Diagnostic & Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).

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.

Prior to PAS, all participants will be assessed for potential contraindications to TMS using a safety-screening questionnaire. This screen as well as the PAS assessments will be performed by personnel with experience utilizing this technique in individuals with PSD. Single pulse cortical stimulation will be delivered using a Bi-Stim module magnetic stimulator (The Magstim Company Limited; Whitland, UK) with a figure-of-eight coil (P/N 3190; 70mm outer diameter of each winding; maximal output of 2.2T). We will use a combination of on-line surface electromyography (sEMG) recordings to view peak-to-peak motor evoked potential (MEP) amplitude and a neuro-navigation system to identify the optimal coil position for stimulation of the abductor pollicus brevis (APB) muscle. The neuro-navigation system consists of a stereotaxic passive marker and camera system (Polaris Vicra P6, NDI, Waterloo, Ontario, Canada) and Brainsight software (Rogue Research Inc.; Montreal, Quebec, Canada), which will allow us to track the location of the figure-of-eight coil and ensure consistency during resting motor threshold (RMT) and SI1mV (stimulus intensity necessary to induce a 1-millivolt MEP response) assessments. In order to locate the APB muscle 'hotspot' we will use a suprathreshold stimulation intensity on the hand area of the primary motor cortex to elicit MEP's of the APB muscle. The area on the hand knob of the motor cortex that produces the largest and most consistent MEP's of the APB muscle will be marked as the 'hotspot' using the neuro-navigation system. After locating the participant's APB muscle 'hotspot' we will then assess the participant's RMT. We define the RMT as the amount of TMS output (expressed in percentage of maximal stimulator output [%MSO]) necessary to induce an

MEP that exceeds or is equivalent to a peak-to-peak amplitude of 50μV (.05mV) in 50% of stimulations. To estimate RMT, we will utilize an automated version of a simple adaptive parameter estimation by sequential testing (SA-PEST) procedure developed at MUSC. [47]

Following RMT assessment, we will assess the participant's SI_{1mV}. The same 'hotspot' location and SA-PEST procedure will be used to determine the participant's SI_{1mV}, however the SA-PEST program will be set to search for MEP amplitudes of approximately 1-mV. Once established, the SI_{1mV} will be used as a primary measure of corticospinal excitability. Using the %MSO of the SI_{1mV} we will then collect 20 test MEP's at a rate of 0.25Hz. Once MEP's are collected, participants will be set-up for peripheral nerve stimulation. Stimulation of the median nerve of the non-dominant arm will be delivered via constant current stimulator (DS7A; Digitimer, Hertfordshire, UK). Bipolar electrodes will deliver a 200μs square wave pulse at an intensity equal to 300% sensory perceptual threshold. Perceptual threshold will be determined each session and will be defined before any stimulation protocols are commenced. Single pulse TMS will be applied to the APB muscle representation on the contralateral motor cortex 25ms (ISI25) after the delivery of median nerve stimulation. A train/delay generator (Digitimer, Hertfordshire, UK) will trigger paired peripheral nerve stimulation and brain stimulation. A total of 200 paired stimuli will be delivered at rate of 0.25 Hz, resulting in a total stimulation time of ~14 minutes. The 20 test MEP's will be reassessed immediately after PAS, and then every 15 minutes for one hour.

We will utilize the PAS measures at baseline, after 2,4,6,8,10 and 12 weeks of treatment (or control) as well as at the follow-up time point to assess whether the interventions change PAS measured neuroplastic potential. We will use PAS to assess cortical excitability (SI_{1mV}) as well as neuroplastic potential (represented by mean normalized post-stimulation MEP amplitude). We will compare PAS measures at baseline to after either POWER or control. We will also compare repeated PAS measures in patients with and without PSD (Aim 2) to determine whether PSD inhibits neuroplasticity, and if effective treatments reverse the impaired potential for plasticity.

Electromyographic assessment: Surface electromyography (sEMG) will be collected using 2cm by 2cm surface recording electrodes and will be placed perpendicular to the orientation of the fibers of the APB muscle belly, on the participant's non-dominant hand. Prior to sEMG placement the site of the APB muscle will be lightly abraded and cleaned with pre-packaged alcohol swabs. All EMG signals will be collected using Spike2 v7.12 software (Cambridge Electronic Design; Cambridge, UK) and will be amplified (x1000) and bandpass- filtered (100-2000 Hz) using a CED 1902 amplifier (Cambridge Electronic Design; Cambridge, UK), and sampled at 5000 Hz using CED Micro 1401-3 data acquisition unit (Cambridge Electronic Design; Cambridge, UK). Data will be saved directly to a network drive for offline analysis. During all stimulation protocols sEMG activity will be continuously monitored in order to ensure that the APB muscle is not voluntarily active.

Exercise Tolerance Testing: Prior to training, a bicycle ergometry protocol modified from the LEAPS trial [8] will be used to assess exercise tolerance prior to study inclusion. The protocol will be overseen by a physician and will commence with the subject seated quietly for two minutes. Exercise will begin with the subject pedaling at ~60 revolutions per minute (RPM) and 0 Watts (W) of workload, with workload will be increased by ~15 W every 3 minutes. If the pedal cadence drops below 50 RPM, additional reminders will be given. Testing continues until maximal effort is achieved. The test will be terminated prior to achieving maximum effort for predefined symptomatic, clinical, and electrocardiographic criteria. Symptom-related reasons for termination include angina, dyspnea, and fatigue.

Fatigue is defined as either voluntary exhaustion or inability to maintain a minimum cycling cadence of 40 RPM. Clinical criteria for termination include: 1) Hypertension: ≥ 220/120 mmHg, or 2) Hypotension: a drop in diastolic blood pressure >20 mmHg, and O2 saturation <85%. Electrocardiogram criteria include: 1) ≥ 1 mm horizontal or down sloping ST segment depression, 2) sustained paroxysmal ventricular tachycardia (>30 beats), and 3) sustained paroxysmal supraventricular tachycardia (>30 beats). If the test is terminated because of electrocardiographic findings, the subject will be managed medically as needed, referred for care, and disapproved for participation. Resting blood pressure and heart rate will be obtained prior to initiation of exercise as well as after the subject has been sitting on the stationary bicycle for 1 minute. During the exercise test, blood pressure readings will be obtained every 3 minutes. Heart rate will be obtained from the 12-lead EKG. Maximal heart rate will be recorded as the highest heart rate achieved during the exercise tolerance test.

Subject monitoring during testing and training: Blood pressure (BP) and heart rate (HR) will be monitored prior to, during, and at completion of each session. Subjects' resting diastolic BP must be <100 mmHg, systolic < 200 mmHg, and heart rate <110 beats/min to begin the testing. [74] Criteria for termination include subject complaints of shortness of breath, light-headedness, confusion, severe headache, or dyspnea; onset of angina; excessive blood pressure (systolic BP > 200mm Hg, diastolic BP >110 mm Hg), or drop in systolic BP >10 mm Hg and inappropriate bradycardia (drop in heart rate >15 bpm).

Experimental protocol for walking data collection: At the beginning of the first training session of every other week (bi-weekly), subjects will walk on a 10m. long gait mat (GaitRite) to measure self-selected and fastest comfortable walking speed and other spatiotemporal parameters. Subjects will be permitted a practice trial, and then be asked to complete three trials at each speed. For all trials, subjects will wear their own shoes and be asked to walk without an assistive device or ankle-foot orthosis. A safety harness mounted to the ceiling will protect the subject but will only support their body weight in the case of a loss of balance. A physical therapist will be present for all testing sessions as needed.

Post-stroke Optimization of Walking using Explosive Resistance (POWER) training: Individuals with chronic post-stroke hemiparesis will undergo training to improve muscle power generation for 12 weeks (3 times/week) that includes both resistive and task-specific elements. Session duration will be ~60 minutes (inclusive of rest intervals) although the total time will depend on the amount of rest needed for a given individual. Training will include five distinct resistance activities aimed at improving muscle power-- each previously reported to contribute to improved walking (Table 1). Sit to stand and leg press exercises are elements of programs shown to be effective in improving strength and walking performance in the post- stroke population. [48] Repeated step-up training using a single riser targets both eccentric and concentric training in both the sagittal and frontal planes. As possible for individual subjects, we will utilize a step height higher than standard community steps (10") to further challenge neuromuscular requirements of the task. Calf raises (i.e. plantar flexion) will be performed on a small step so as to allow for adequate range of motion. In addition, our pilot data demonstrate that jump training, focused on lower extremity muscle power generation, is part of a comprehensive program that improves gait speed in people with post-stroke gait deficits. Sit to stand, step-up and calf raise activities will be performed within the novel overground body-weight support (BWS) environment enabled by the Zero-G (ZeroG, Bioness Inc., Valencia, CA), whether receiving support or not, to provide the maximum safety possible.

During the initial training session, subjects will perform the individual component tasks beginning with least amount of BWS (or highest load) required for successful completion of

the required number of repetitions in order to match the participant's ability to the difficulty of the task. [49] BWS will be progressively reduced to determine the minimum support necessary to complete each task. Participants will be progressed within each task by decreasing BWS by 5% of body mass (or adding 5% load for leg press) upon successfully meeting the goals for progression (see Table 1). An adjustable weighted vest will be utilized to increase mass by 5% during training once support is not required for successful task completion. Subjects will not be permitted to use assistive devices and physical assistance will not be provided during training.

Sit to stand, leg press, step-up and calf raise activities will be performed under two conditions within each training session. Condition 1 will include performing two sets of ten repetitions with the targeted amount of resistance for the given session and based on rate of progression throughout training. Condition 2 will require the participant to perform as many repetitions as possible during a 20 second period utilizing either 80% of the resistance from Condition 1 or an increase in BWS of 20%. This condition is designed to encourage high velocity and hence high-power output contractions. Given our focus on muscle power generation, all participants will be instructed to perform the concentric portion of each exercise at maximum velocity regardless of the prescribed condition, followed by a controlled eccentric contraction. This approach is adapted from programs specifically targeting power training in aging populations with mobility deficits and shown to result in significant increases in peak power generation when compared to slower velocity training, while achieving similar gains in strength. [50,51,52]

For jump training, subjects will be familiarized with the equipment and, during the initial training session, will complete a total of 30 (3 sets of 10) bilateral ground contacts (jumps). We will begin the first session at a resistance of ~20% of body mass. Based on individual subject ability, external resistance will be increased (or decreased) and resistance documented. The number of jumps will be increased to 45 in week two and to 60 thereafter (the goal being to complete the prescribed # of jumps in ≤ 3 sets). Upon successful completion of at least 60 ground contacts (e.g. complete clearance from foot plate; Figure 5), resistance will be increased in increments of 5 lbs. or 5% body mass, whichever is greatest. As subjects feel comfortable, and no later than week 4, unilateral jump training will be performed using each leg, the goal being to progress to a reciprocating jumping pattern (i.e. alternating legs each jump for a total of 60 jumps per leg). Throughout the training protocol, a minimum of two sessions at a given resistance will be required before load is increased and resistance will be held consistent between limbs throughout the training program. Session intensity will be systematically progressed and modified by changing either the applied resistance or the number of ground contacts.

Figure 5: Exercise apparatus used for jump training

Progressive loaded overground fast walking: As part of each training session, subjects will perform 10 trials of fast walking (10 meter per trial). These trials are intended to emphasize the task-specific lower extremity power generation required to accomplish increased walking speeds. Subjects will be asked to complete all trials without an assistive device or ankle-foot orthosis at speeds ≥ 125% of self-selected overground velocity. Although we will

not allow the use of an AFO, subjects will be permitted to wear an ankle brace for medial-lateral support (AirCast®) that allows for plantarflexion and dorsiflexion voluntary movements. Subjects will walk over our instrumented walkway (GaitRite) so as to provide real time feedback of speed as well as spatio- temporal parameters of walking for each trial. These trials will also be performed in the ZeroG harness to protect the subject in the case of a loss of balance as well as to provide body-weight support as needed to facilitate walking at the required speeds. After each session, the average speed will be calculated and compared to the self-selected speed. When the average speed exceeds 125% of self-selected speed, we will decrease BWS by 5% for the next training session. At the point when subjects are able to successfully exceed 125% of self-selected speed without body-weight support, a weighted vest will be worn and mass systematically added to allow progression. Note that in order to provide the optimal stimulus for increasing propulsion, we will provide an amount of BWS to offset to the added mass. This has been shown to engage the muscles most responsible for generating propulsion to a greater extent [53] and should optimize the power training stimulus for the muscles generating propulsion.

It is important to point out that progression for muscle power training and overground stepping will be accomplished via reduction in BWS (or added mass) as tolerated, allowing for increased "resistance" and graded exercise. The overground permissive environment allows safe training without assistive devices or and allows determination of the precise ability level of the individual for a task. In creating a constant permissive environment, we are able to identify precisely how much support is required for independent completion of the task while simultaneously eliminating falls risk. This environment allows the participant to engage in therapy at a consistently more challenging level than is allowed in conventional rehabilitation. This approach is based on a philosophy known as the "challenge point framework", which theorizes that one's ability level is defined by the level of difficulty at which one has an equal (50%) chance of success or failure, [49] a level of difficulty that is rarely matched in clinical rehabilitation due to increased potential for falls.

Attention Control (Stretching): Stretching is being used as an attention control condition for POWER training. Control subjects will participate in a stretching protocol for the same duration (i.e. 60 minutes per session) and frequency (3 days per week) for 12 weeks to ensure that they have equal interaction with the study staff and controlling for the effects of repeated social interaction on depressive symptoms. The stretching program is a modified protocol previously implemented in a post-stroke population and designed for individuals 50 years of age and older and will include activities targeting upper and lower extremity flexibility. [54] Specifically, subjects in this group will perform traditional stretching movements targeting flexors and extensors of the knees, ankles and hips bilaterally. In addition, low back rotations, bridging, prone extensions and hip abduction will also be performed. Upper extremity movements will include shoulder flexion, horizontal flexion/abduction, internal and external rotation as well as wrist flexion and extension. As individual levels of flexibility increase, the level of difficulty will be increased accordingly. Heart rate responses to the stretching program will be intentionally kept below 40% heart rate reserve. The stretching will be overseen by a licensed physical therapist or exercise physiologist and consistently monitored throughout the period of training.

*** To provide the best care possible, those initially randomized to the control group will be offered the opportunity to re-enroll into POWER training should they still meet criteria for depression at the follow-up time point.

Dynamometric Assessment: Isometric and isotonic assessments will be performed for knee extension and ankle plantar flexion at bi-weekly intervals throughout POWER using a

Biodex isokinetic dynamometer (Biodex Corp., Shirley, NY). Prior to testing, each subject will go through a period of familiarization and warm-up consisting of 5 minutes of cycling and three sub-maximal contractions. During isometric testing, maximum voluntary isometric contraction (MVIC) will be defined as the highest torque achieved during 3 maximal contractions (~3 sec contractions separated by a minimum of 60 seconds rest). If MVIC values during the three trials differ by more than 5%, additional contractions will be performed. During isotonic testing, peak power will be assessed using 40% of MVIC. Differences in lower extremity maximal velocity are shown to occur at relatively low external forces (e.g. 40% 1 RM) and are most closely associated with gait velocity in older individuals. [51] To optimize reliability of the testing, each test will be repeated 3 times. If the coefficient of variation among the 3 highest powers is > 10%, additional contractions will be performed. Power-angle curves will be plotted and the peak powers recorded. During all dynamometric testing, subjects will be instructed to (1) develop torque as fast as possible and (2) produce a maximal contraction. Subjects will be given an auditory cue and receive continuous visual feedback. All contractions will be performed with subjects positioned in the dynamometer and the axis of the dynamometer aligned with the joint axis of rotation. Proximal stabilization will be achieved with straps at the chest, hips, and knee as appropriate. In order to increase sensitivity, the force transducer signal will be amplified and fed into a data acquisition unit (Lab View Inc.) and corrected for the effects of gravity.

11.0 Specimen Collection and Banking

N/A

12.0 Data Management

Data Analysis Plan: We will compare the effects of POWER training (vs. control) on HRSD scores. We will also determine response (≥50% reduction in symptoms) and remission (HRSD < 10) rates following training and at a six-month follow-up. We will utilize repeated measures mixed effects models to assess significant changes in outcomes between groups. Time and group will serve as dependent variables, as well as their interactions. A random intercept term will be included in the model to account for clustering within subjects. Various error structures associated with the repeated measures will be considered (e.g. compound symmetry vs. auto-regressive).

We will determine if PSD limits response to treatment by making between group comparisons of change (post-pre) in outcomes in depressed vs. non-depressed subjects utilizing repeated measures mixed models. Time (seven occasions), group (depressed vs. non-depressed) and their interaction will serve as dependent variables. Three primary dependent variables of interest here are, self-selected walking speed (SSWS) and paretic leg power generation. A random intercept term will be included in the model to account for clustering within subjects. Various error structures associated with the repeated measures over time will be considered (e.g. compound symmetry vs. auto-regressive). Analyses incorporating differences in outcomes as dependent variables will examine whether changes over time are more pronounced in depressed versus non-depressed subjects as well as whether changes are more pronounced in depressed subjects with the greatest improvement in HRSD. These models will also incorporate random subject effects to account for within-subject dependence. To determine associations between changes in outcomes, we will look at the relationships between outcomes using Pearson or Spearman correlations, depending on the distribution of the data. Further, we will use segmented (joint-point) regression to estimate if specific thresholds exist that mark in individual subjects where HRSD starts improving (decreases) and other outcomes start to improve (increase) to help us understand

if there is a critical point of change in HRSD that is important for facilitating functional improvements. The purpose of using the segmented regression is to see if HRSD scores either plateau or change direction at a given point. The segmented regression model will essentially fit two linear models that have different slopes and intercepts but meet at a point of time. This will be achieved through inclusion of a dummy variable and its interaction with time in the model. The dummy variable will take the value 0 for time points below the threshold and 1 above. The threshold, namely the time, at which the model changes direction will be assumed unknown. Therefore, this model will be a non-linear regression model. We have written a macro in SAS to fit such models. This macro also allows for higher-order polynomials. Our intention is to fit random effects models, calling PROC NLMIXED in our macro. Other covariates can also be included in this approach. The purpose of the segmented regression model is to identify the earliest time at which there is maximum effect.

All efforts will be taken to minimize dropouts. If dropouts occur, we will attempt to determine the reason for dropout. If the dropouts occur at random, the mixed effects model can account for the missing data. However, if the dropouts are found to be treatment related, they will be treated as non-ignorable missing data and appropriate missing data methods will be applied and multiple imputations considered.

Sample size determination and Statistical Approach: A total of 50 post-stroke subjects will be recruited. For Aim 1, 32 subjects with PSD will participate in either POWER training or control intervention (n=16 per group). These analyses will rely on longitudinal measures and we assume (based on experience with this intervention) that no more than 15% will fail to complete all assessments. This is an extremely conservative approach in that none of the subjects in our pilot trial withdrew from treatment. With 16 subjects enrolled per group and a 15% attrition rate over time (resulting in complete data on 13 subjects per group), we would have at least 80% power to detect a minimum difference in the change in HRSD from baseline to the end of the study of 2.94 (change in pilot data = 6.6) with a s.d. of 5.3 (at 5% significance level). Since this is a longitudinal study, we also incorporated an autocorrelation (AR(1)) of 0.5 for 10 measurements within individuals. The published studies report treatment effect sizes ranging from 0.6 to 0.9, which are more conservative. In our preliminary data, we observed an effect size of 1.19 (95% CI 0.98 to 1.36) for improvement in depression severity. To detect this effect we will have more than 90% power. For Aim 2, with baseline data from n=26 subjects, we will have 80% power to detect a minimum difference (pre-post) of 0.13 m/s for SSWS (s.d. = 0.2 m/s) and 17.88 ft/lb for muscle strength (s.d=31.9 ft/lb) using a longitudinal approach with an autocorrelation (AR (1)) of 0.5 for 10 measurements within individuals. In the statistical analysis for both aims, we will summarize the longitudinal data using Spaghetti plots. If the spaghetti plots suggest linear or quadratic trend we will include these in the model along with appropriate interactions and random effects. We will perform appropriate model diagnostics and, if needed, consider transformations to achieve normality. To reduce potential heterogeneity in the data, secondary analysis will adjust for covariates such as depression level.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

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.

Adverse events**:** An adverse event will be defined as any expected or unexpected harmful event observed in subjects enrolled in the approved project. Adverse events do not necessarily have a causal relationship with aspects of the treatment or be related to study procedures. A serious adverse event is any event that results in death, a life-threatening situation, hospitalization or prolonged hospitalization, persistent or significant disability/incapacity or a congenital anomaly/birth defect or requires medical intervention to prevent one of the outcomes listed above. Serious adverse events require prompt reporting to the sponsor and the IRB. Important medical events that may not result in death, be life-threatening, or require hospitalization may also be considered serious adverse events when, based on appropriate medical judgment of the study physician, they could jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes in this definition. The data and safety monitoring plan for this study will include subject monitoring for adverse events, review of these events by the study team, study physician and IRB.

Subject monitoring**.** At each study visit, subject voluntary reporting of potential adverse events will be encouraged and events of interest will elicit specific follow-up to include: falls, orthopedic injuries and new or exacerbating pain. During training, safety monitoring will include HR, blood pressure, and continuous observation for other signs or symptoms of cardiorespiratory insufficiency, worsening neurologic impairments or orthopedic injury. In addition, any adverse responses to TMS will be closely monitored. Adverse events will be followed until resolution determined by a physician according to type, severity and need for treatment. Any causal relationship with the intervention or impact on the study intervention, whether anticipated or not will be specifically documented.

Data Safety & Monitoring Plan:

Trial Management: The proposed study will be managed through the Department of Health Sciences & research at the Medical University of South Carolina (MUSC). All data will be collected and tracked using only the assigned study ID of each participant and the cross-walk linking the study ID to each participant's personal identifying data will be kept confidential and locked in a secured location. All study data will be collected by the appropriate individual (research staff, PIs, Co-Is). Data will be collected using standardized paper and electronic forms and will be securely transferred to the data entry location. Research staff will transcribe any paper data into a REDCap data capture system (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SAS/STAT and SPSS); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data).

Data Quality Assurance: Validity and data integrity will be checked on an ongoing basis through the use of data audits. The study statistician (Ramakrishnan) will supervise quarterly data quality assessments (i.e., examination of the outcomes database(s) for missing data, unexpected distributions or responses, and outliers) performed by the study research staff. Accuracy and completeness of the data collected will be ensured by bi-weekly review. A 10% random sample of the primary source document will be cross-checked with the database on a quarterly basis. If

inaccuracies exceed 2%, then a second 10% will be randomly chosen for audit. Should data discrepancies be discovered, they will be resolved using original source documents. The REDCap system does not accept outliers, illogical response patterns, etc. The PI will have bi-weekly meetings with the research staff to discuss qualitative comments received during treatments and data collection sessions as well as any problems in data collection or entry. The statistician will periodically examine the database to look for irregularities. Initial data analyses will examine distributions of variable scores and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these.

All serious adverse events will be reported to the MUSC Institutional Review Board (IRB) within 24 hrs. Follow-up of all serious adverse events will be reported as well. Based on our previous studies involving exercise and/or TMS in individuals post-stroke, we anticipate the serious adverse event rate to be extremely low.

Adverse Event Monitoring and Trial Safety: The proposed methodologies are all non-invasive and, as such, involve minimal physical risk to participants. However, adverse events will be monitored throughout the study and all events will be followed to resolution or stabilization. Adverse events will be coded on a weekly basis and the research staff will prepare a summary of all adverse events. The PI will review this during weekly study meetings (or before if more urgent). Serious adverse events are defined as events, related or unrelated, that require or prolong hospitalization or result in congenital defects, death, disability, cancer, overdose, development of drug dependency or abuse, or any other life-threatening event. The Institutional Review Board (IRB) of the Medical University of South Carolina (MUSC) will be immediately informed of any serious adverse events as soon as the PIs, Co-Is, or study staff are made aware of it and a written report will be filed within 72 hours. The research staff will be instructed not to reveal whether a person is a participant in the study and will report to the PIs any outside requests for information about a participant or any breaches in confidentiality. All requests by participants' physicians and other medical providers will be referred directly to the PIs.

Data Safety & Monitoring and Study Implementation: The PI (Chris Gregory, Ph.D., P.T) will be responsible for monitoring the trial. The PI will perform biweekly evaluations of the data safety by examining adverse events summary prepared by research staff. Specifically, the PI will work with the study statistician and IRB to define acceptable frequency of adverse events and serious adverse events.

14.0 Withdrawal of Subjects (if applicable)

Participation in this study is completely voluntary and participants may decide to stop taking part in this study at any time. In addition, there may be circumstances where the investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in the best interest of the participant. Examples of such circumstances include those that represent a perceived health risk to the individual (e.g., chronic elevation in resting blood pressure or significant unexplained increase in depressive symptoms). If such a circumstance does occur, participants will be notified by the research staff of the decision and recommendations for follow-up will be provided to the individual. If the decision if made for a participant to withdraw (whether by the individual or the research staff) no further data will be collected. However, data collected to date will still be analyzed using intent-to-treat analyses.

15.0 Risks to Subjects

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 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).

At any point during the study, should a participant complete the HRSD and answer questions indicating very severe depression (>22) or answer any questions on the HRSD or PHQ-9 indicating any suicidal ideation, thoughts, or plan, they will be immediately referred for clinician evaluation. This includes those patients whose symptoms may worsen during the course of the study. A licensed psychiatrist (Dr. George or one of his colleagues) will be available during all depression assessments if further evaluation is necessary. In the event of an incident during treatment or training that a clinician is not immediately available, the participant will be escorted to the emergency department for further evaluation.

16.0 Potential Benefits to Subjects or 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.

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 psychological and locomotor function. 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

17.0 Sharing of Results with Subjects

None of the individual data collected as part of this study will be shared. However, aggregate data generated for the purpose of scientific publication will be made available to participants once the final data analyses are completed.

18.0 Drugs or Devices (if applicable)

N/A

References

1. Lokk J, Delbari A. (2010). Management of depression in elderly stroke patients. *Neuropsychiatric disease and treatment*;6:539-549.
2. Hadidi N, Treat-Jacobson DJ, Lindquist R. (2009). Poststroke depression and functional outcome: a critical review of literature. *Heart & lung : the journal of critical care.* Mar-Apr;38(2):151-162.
3. Hackett ML, Yapa C, Parag V, Anderson CS. (2005). Frequency of depression after stroke: a systematic review of observational studies. *Stroke; a journal of cerebral circulation.* Jun;36(6):1330-1340.
4. Jia H, Damush TM, Qin H, Ried LD, Wang X, Young LJ, Williams LS. (2006). The impact of post-stroke depression on healthcare use by veterans with acute stroke. Stroke. Nov; 37(11):2796-801.
5. Hackett ML, Anderson CS, House AO. (2004). Interventions for treating depression after stroke. *Cochrane database of systematic reviews (Online).*(3):CD003437.
6. Hackett ML, Anderson CS, House AO, Xia J. (2009). Interventions for Treating Depression After Stroke. *Stroke; a journal of cerebral circulation.* May 14.
7. Paolucci S, Antonucci G, Pratesi L, Traballesi M, Grasso MG, Lubich S. (1999). Poststroke depression and its role in rehabilitation of inpatients. *Archives of physical medicine and rehabilitation.* Sep 80(9):985-990.
8. Duncan PW, Sullivan KJ, Behrman AL, et al (2007). Protocol for the Locomotor Experience Applied Post-stroke (LEAPS) trial: a randomized controlled trial. BMC Neurol; 7-39.
9. Winstein CJ, Wolf SL, Dromerick AW, Lane CJ, Nelsen MA, Lewthwaite R, Cen SY, Azen SP; Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) Investigative Team. (2016). Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial. JAMA Feb 9; 315(6):571-81.
10. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, Nichols-Larsen D; EXCITE Investigators. (2006). Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. Nov 1;296(17):2095-104.
11. Singh NA, Stavrinos TM, Scarbek Y, Galambos G, Liber C, Fiatarone Singh MA. (2005). A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. J Gerontol A Biol Sci Med Sci.
12. Aidar FJ, de Matos DG, de Oliveira RJ, Carneiro AL, Cabral BG, Dantas PM, Reis VM. (2014). Relationship between Depression and Strength Training in Survivors of the Ischemic Stroke. J Hum Kinet. Nov 12;43:7-15.
13. Morgan P, Embry A, Perry L, Holthaus K, Gregory CM. (2015). Feasibility of lower-limb muscle power training to enhance locomotor function poststroke. J Rehabil Res Dev.;52(1):77-84.
14. S Aaron, J Hunnicutt, AE Embry, MG Bowden and CM Gregory. POWER Training in Chronic Stroke Individuals: Differences between Responders and Non-responders. *Topics in Stroke Rehabilitation.* 2017 Oct;24(7):496-502.
15. J Hunnicutt, S Aaron, AE Embry, B Cence, P Morgan, MG Bowden and CM Gregory. The Effects of POWER Training in Young and Older Adults Post-stroke. *Stroke Research & Treatment*. 2016; PMID: 27493828

16. Player MJ, Taylor JL, Weickert CS, Alonzo A, Sachdev P, Martin D, Mitchell PB, Loo CK. (2013). Neuroplasticity in depressed individuals compared with healthy controls. Neuropsychopharmacology. Oct; 38(11):2101-8.
17. Player MJ, Taylor JL, Weickert CS, Alonzo A, Sachdev PS, Martin D, Mitchell PB, Loo CK. (2014). Increase in PAS-induced neuroplasticity after a treatment course of transcranial direct current stimulation for depression. J Affect Disord; 167:140-7.
18. Gresham GE, Kelly-Hayes M, Wolf PA, Beiser AS, Kase CS, D'Agostino RB. (1998). Survival and functional status 20 or more years after first stroke: the Framingham Study. *Stroke; a journal of cerebral circulation.* Apr;29(4):793-797.
19. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. (1995). Recovery of walking function in stroke patients: the Copenhagen Stroke Study. *Archives of physical medicine and rehabilitation.* Jan;76(1):27-32.
20. Perry J, Garrett M, Gronley JK, Mulroy SJ. (1995). Classification of walking handicap in the stroke population. *Stroke; a journal of cerebral circulation.* Jun;26(6):982-989.
21. Bohannon RW, Horton MG, Wikholm JB. (1991). Importance of four variables of walking to patients with stroke. *International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue internationale de recherches de readaptation.*;14(3):246-250.
22. Kvelde T, Lord SR, Close JC, Reppermund S, Kochan NA, Sachdev P, Brodaty H, Delbaere K. (2015). Depressive symptoms increase fall risk in older people, independent of antidepressant use, and reduced executive and physical functioning. Arch Gerontol Geriatr. Jan-Feb;60(1):190-5.
23. Kvelde T, McVeigh C, Toson B, Greenaway M, Lord SR, Delbaere K, Close JC. (2013). Depressive symptomatology as a risk factor for falls in older people: systematic review and meta-analysis. J Am Geriatr Soc. May;61(5):694-706.
24. National Institute on Aging (1999). Exercise: A Guide From the National Institute on Aging. Bethesda, MD: National Institute on Aging, National Institutes of Health.
25. Teixeira-Salmela LF, Olney SJ, Nadeau S, Brouwer B (1999). Muscle strengthening and physical conditioning to reduce impairment and disability in chronic stroke survivors. Arch Phys Med Rehabil. Oct;80(10):1211-8.
26. Lee MJ, Kilbreath SL, Singh MF, Zeman B, Davis GM (2010). Effect of progressive resistance training on muscle performance after chronic stroke. Med Sci Sports Exerc. Jan;42(1):23-34.
27. O'Connor PJ, Herring MP, Caravalho A. (2010). Mental health benefits of strength training in adults. American Journal of Lifestyle Medicine. 4(5); 377-396.
28. Martin DM, Alonzo A, Ho KA, et al. (2012). Continuation transcranial direct current stimulation for the prevention of relapse in major depression. *Journal of affective disorders.* Nov 9.
29. Normann C, Schmitz D, Furmaier A, Doing C, Bach M. (2007). Long-term plasticity of visually evoked potentials in humans is altered in major depression. *Biological psychiatry*;62(5):373-380.
30. Nissen C, Holz J, Blechert J, et al. (2010). Learning as a model for neural plasticity in major depression. *Biological psychiatry.* Sep 15;68(6):544-552.
31. Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain : a journal of neurology. Mar 2000;123 Pt 3:572-584.

32. Cooke SF, Bliss TV. Plasticity in the human central nervous system. Brain : a journal of neurology. Jul 2006;129(Pt 7):1659-1673.
33. Player MJ, Taylor JL, Alonzo A, Loo CK. Paired associative stimulation increases motor cortex excitability more effectively than theta-burst stimulation. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. Nov 2012;123(11):2220-2226. PMID 22608487
34. Keefe RSE, Kraemer HC, Epstein RS, et al. Defining a Clinically Meaningful Effect for the Design and Interpretation of Randomized Controlled Trials. Innovations in Clinical Neuroscience. 2013;10(5-6 Suppl A):4S-19S. PMID 23882433
35. Bowden MG, Behrman AL, Neptune RR, Gregory CM, Kautz SA. (2013). Locomotor rehabilitation of individuals with chronic stroke: difference between responders and non-responders. *Archives of physical medicine and rehabilitation. 94(5); 856-62*.
36. Ramasubbu R, Robinson RG, Flint AJ, Kosier T, Price TR. (1998). Functional impairment associated with acute poststroke depression: the Stroke Data Bank Study. J Neuropsychiatry Clin Neurosci.
37. George MS, Lisanby SH, Avery D, et al. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Archives of general psychiatry.* May;67(5):507-516.
38. de Vries PM, de Jong BM, Bohning DE, Walker JA, George MS, Leenders KL. (2009). Changes in cerebral activations during movement execution and imagery after parietal cortex TMS interleaved with 3T MRI. *Brain research.* Aug 18;1285:58-68.
39. Mantovani A, Pavlicova M, Avery D, Nahas Z, McDonald WM, Wajdik CD, Holtzheimer PE 3rd, George MS, Sackeim HA, Lisanby SH. (2012). Long-term efficacy of repeated daily prefrontal transcranial magnetic stimulation (TMS) in treatment-resistant depression. Depress Anxiety. Oct;29(10):883-90.
40. Johnson KA, Baig M, Ramsey D, Lisanby SH, Avery D, McDonald WM, Li X, Bernhardt ER, Haynor DR, Holtzheimer PE 3rd, Sackeim HA, George MS, Nahas Z. (2013). Prefrontal rTMS for treating depression: location and intensity results from the OPT-TMS multi-site clinical trial. Brain Stimul. Mar;6(2):108-17.
41. Trajković G, Starčević V, Latas M, Leštarević M, Ille T, Bukumirić Z, Marinković J. Reliability of the Hamilton Rating Scale for Depression: a meta-analysis over a period of 49 years. Psychiatry Res. 2011 Aug 30;189(1):1-9.
42. Shumway-Cook A, Woollacott M (2001). Motor Control: Theory and Practical Applications. Philadelphia: Lippincott Williams and Wilkins.
43. Mudge S, Stott NS, Walt SE (2007). Criterion validity of the StepWatch Activity Monitor as a measure of walking activity in patients after stroke. Arch Phys Med Rehabil; 88:1710-5.
44. Solway S, Brooks D, Lacasse Y, Thomas S (2001). A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest; 119:256-70.
45. Wade D (1992). Measurement in neurological rehabilitation. New York: Oxford Univ Press.
46. Rossier P, Wade DT (2001). Validity and reliability comparison of 4 mobility measures in patients presenting with neurologic impairment. Arch Phys Med Rehabil; 82:9-13.

47. Borckardt, J. J., Nahas, Z., Koola, J., & George, M. S. (2006). Estimating resting motor thresholds in transcranial magnetic stimulation research and practice: A computer simulation evaluation of best methods. *The Journal of ECT, 22*(3), 169-175.
48. Tung FL, Yang YR, Lee CC, Wang RY (2010). Balance outcomes after additional sit-to-stand training in subjects with stroke: a randomized controlled trial. Clin Rehabil.; 24:533-42.
49. Guadagnoli MA, Lee TD (2004). Challenge point: a framework for conceptualizing the effects of various practice conditions in motor learning. J Mot Behav; 36:212-24.
50. Fielding RA, LeBrasseur NK, Cuoco A et al (2002). High velocity power training increases skeletal muscle strength and power in community-dwelling older women. J Am Geriatr Soc; 50: 655–662.
51. Bean J, Kiely DK, Herman S et al (2002). The relationship between leg power and physical performance in mobility limited elders. J Am Geriatr Soc; 50: 461–467.
52. Bean JF, Leveille SG, Kiely DK, Bandinelli S, Guralnik JM, Ferrucci L (2003). A comparison of leg power and leg strength within the InCHIANTI Study: which influences mobility more? J Gerontol A Biol Sci Med Sci; 58A(8):728-733.
53. McGowan CP, Neptune RR, Kram R (2008). Independent effects of weight and mass on plantar flexor activity during walking: implications for their contributions to body support and forward propulsion. J Appl Physiol. Aug; 105(2):486-94.
54. Luft AR, Macko RF, Forrester LW, et al. (2008). Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. Stroke. Dec;39(12):3341-3350.
55. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S. (2004). Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A. Mar 2; 101(9):3316-21.
56. Bobath B. Adult Hemiplegia Evaluation and Treatment. 3rd ed. (1990) Oxford: Butterworth Heinemann.
57. Flansbjer UB, Miller M, Downham D, Lexell J (2008). Progressive resistance training after stroke: effects on muscle strength, muscle tone, gait performance and perceived participation. J Rehabil Med.; 40(1):42–48.
58. Moreland JD, Goldsmith CH, Huijbregts MP, et al (2003). Progressive resistance strengthening exercises after stroke: a single-blind randomized controlled trial. Arch Phys Med Rehabil.; 84(10):1433–1440.
59. Sharp SA, Brouwer BJ (1997). Isokinetic strength training of the hemiparetic knee: effects on function and spasticity. Arch Phys Med Rehabil.; 78(11):1231–1236.
60. Beloosesky Y, Streifler JY, Burstin A, Grinblat J (1995). The importance of brain infarct size and location in predicting outcome after stroke. Age Ageing. Nov; 24(6):515-518.
61. van Everdingen KJ, van der Grond J, Kappelle LJ, Ramos LM, Mali WP (1998). Diffusion-weighted magnetic resonance imaging in acute stroke. Stroke; 29(9):1783-1790.
62. Hatakenaka M, Miyai I, Sakoda S, Yanagihara T (2007). Proximal paresis of the upper extremity in patients with stroke. Neurology. Jul; 69(4):348-355.

63. Shelton FN, Reding MJ (2001). Effect of lesion location on upper limb motor recovery after stroke. Stroke. Jan.; 32(1):107-112.
64. Chen CL, Tang FT, Chen HC, Chung CY, Wong MK (2000). Brain lesion size and location: effects on motor recovery and functional outcome in stroke patients. Arch Phys Med Rehabil. Apr;81(4):447-452.
65. Yamada K, Ito H, Nakamura H, et al (2004). Stroke patients' evolving symptoms assessed by tractography. J Magn Reson Imaging. 20(6):923-929.
66. Konishi J, Yamada K, Kizu O, et al (2005). MR tractography for the evaluation of functional recovery from lenticulostriate infarcts. Neurology. Jan; 64(1):108-113.
67. Dromerick AW, Reding MJ (1995). Functional outcome for patients with hemiparesis, hemihypesthesia, and hemianopsia. Does lesion location matter? Stroke. Nov; 26(11):2023-2026.
68. Nelles M, Gieseke J, Flacke S, Lachenmayer L, Schild HH, Urbach H (2008). Diffusion tensor pyramidal tractography in patients with anterior choroidal artery infarcts. AJNR Am J Neuroradiol; 29(3):488-493.
69. Pantano P, Formisano R, Ricci M, et al (1996). Motor recovery after stroke. Morphological and functional brain alterations. Brain; 119 (Pt 6):1849-1857.
70. Nepveu JF, Thiel A, Tang A, Fung J, Lundbye-Jensen J, Boyd LA, Roig M. (2017) A Single Bout of High-Intensity Interval Training Improves Motor Skill Retention in Individuals With Stroke. Neurorehabil Neural Repair. Aug;31(8):726-735.
71. Duncan PW, Wallace D, Studenski S, Lai SM, Johnson D (2001). Conceptualization of a new stroke-specific outcome measure: the stroke impact scale. Top Stroke Rehabil; 8:19-33.
72. Duncan PW, Bode RK, Min Lai S, Perera S (2003). Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. Arch Phys Med Rehabil; 84:950-63.
73. Duncan PW, Lai SM, Bode RK, Perera S, DeRosa J (2003). Stroke Impact Scale-16: A brief assessment of physical function. Neurology; 60:291-6.
74. Mahler DA, Froelicher VF, Miller NH (1995). The American College of Sports Medicine's Guidelines for Exercise Testing and Prescription, 5th edition. Philadelphia: Williams & Wilkins.
75. Ross RE, VanDerwerker CJ, Newton JH, George MS, Short EB, Sahlem GL, Manett AJ, Fox JB, Gregory CM. Simultaneous aerobic exercise and rTMS: Feasibility of combining therapeutic modalities to treat depression. Brain Stimul. 2017 Oct 31.
76. VanDerwerker CJ, Ross RE, Stimpson KH, Embry AE, Aaron SE, Cence B, George MS, Gregory CM. Combining therapeutic approaches: rTMS and aerobic exercise in post-stroke depression: a case series. Top Stroke Rehabil. 2017 Oct 6:1-7.
77. Samii A, Wassermann EM, Ikoma K, Mercuri B, George MS, O'Fallon A, Dale JK, Straus SE, Hallett M. Decreased postexercise facilitation of motor evoked potentials in patients with chronic fatigue syndrome or depression. Neurology. 1996 Dec;47(6):1410-4.
78. Roberts DR, Ricci R, Funke FW, Ramsey P, Kelley W, Carroll JS, Ramsey D, Borckardt JJ, Johnson K, George MS. Lower limb immobilization is associated with increased corticospinal excitability. Exp Brain Res. 2007 Aug;181(2):213-20.