Robotic Pedaling Therapy for Targeted Neural

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RESEARCH PROTOCOL

Robotic Pedaling Therapy for Targeted Neural Plasticity

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Project Summary

The aim of this Pilot study is to determine whether robotically targeted lower-limb pedaling therapy can increase the extent of stroke recovery on behavioral measures and induce brain plasticity as measured by functional magnetic resonance imaging (fMRI). Forty (40) adult stroke patients and 80 healthy controls will be enrolled in this study. Of the 40 patients, half will be randomly assigned to the robotically-targeted training ("robotic") group and will receive training on the targeted training task. The other half of the patients will perform a duration-matched aerobic pedaling exercise ("control" group). All stroke patients will be scanned before and after their training program while performing or imagining simple motor tasks. Behavioral assessments of motor and cognitive capacities will be collected at each timepoint. Healthy control subjects enrolled for device testing (20) will receive up to 5 training sessions in a modified robotic paradigm and 1 fMRI scan, in order to investigate motor learning and brain activity in a novel motor control task. Additional healthy pilot subjects (up to 60) will test training protocols and assessments during preparatory design phases of the project.

Background and Significance

Previous studies have shown that robotic therapy can enhance functional and motor recovery in stroke survivors. The best results are from upper-limb therapies designed to incentivize volitional muscle control on the part of the patient, usually in robotically-perturbed reaching tasks. Lower-limb robotic therapies have focused primarily on using robotic exoskeletons to assist motion of the legs during walking, an approach that has been criticized for not requiring volitional control from the patient. Here we plan to adapt the robotically-targeted control incentivization common in upper-limb therapy to a lower-limb pedaling task. A robotic exercise cycle will reward improved activation or control of impaired neural motor circuits, by varying the controlled speed or resistance of the cycle in response to user performance. The patient’s task will be to produce pedal forces in specific directions, or electromyographic signals (EMG) in particular patterns, designed to elicit activity in impaired motor circuits of the brain. We will combine this robotic therapy with behavioral measures of leg function, kinematic measures of leg function during walking, and functional magnetic resonance imaging (fMRI) to determine if the targeted therapy can improve stroke recovery to a greater extent than a simple pedaling exercise. Unlike many previous approaches, the pedaling task could ultimately be used in early- stage recovery, before patients are able to walk. Also, it specifically targets and rewards improvements in volitional control of impaired motor circuits, instead of functional outcomes that may reward compensation rather than true motor recovery.

Specific Aims

To evaluate motor recovery following a targeted robotic training regimen, in comparison to aerobic cycling, in stroke patients with chronic impairment of moderate severity.

To determine if this therapy induces greater brain plasticity in comparison to aerobic pedaling exercise, as measured by functional magnetic resonance imaging (fMRI).

Study Objectives

Primary objective

To examine the effect of a robotic pedaling therapy program that rewards coordinated foot pedal forces and EMG patterns on lower-limb function during pedaling and walking, in comparison to an aerobic pedaling task.

Secondary objective

To examine plasticity changes as measured by fMRI measures before and after robotic pedaling therapy, in comparison to an aerobic pedaling task.

Study Outcomes

Primary outcome

The primary outcome is behavioral gait function, as measured from the Six Minute Walk Test (6MWT), self-selected walking speed (SSWS) and fastest comfortable walking speed (FCWS). Measures of interest will include speed, distance walked, and variability, symmetry and stability of foot placement patterns, as measured by foot-worn inertial motion sensors.

Secondary outcomes

The change in strength of brain activity in affected regions of interest (ROI) within the brain, and the change in laterality index (LI) comparing the same ROI in affected and unaffected hemispheres. Regions of interest include the primary sensorimotor cortex, the supplementary motor area, and the cerebellum.

Normative data on the progression of motor learning (behavioral measures) and brain activity (fMRI) in control subjects of similar age to the stroke-prone population (50-85 years).

Research Design and Methods

Forty (40) adult stroke patients as well as 80 healthy controls will be enrolled in this study. The 40 stroke patients will be subdivided into two equal groups; the “robotic” group will receive the targeted training task, while the “control” group will perform duration-matched aerobic pedaling. 20 healthy controls enrolled (age 50-85) will contribute to a normative data set. They will receive up to 5 training sessions in a modified robotic paradigm and up to 1 fMRI scan. The other healthy control subjects (age 18-50) will participate as pilot subjects during early phases while the device and therapeutic task specifications are developed, and throughout the project while the device and tasks are refined. These pilot subjects will test the robotic device; help us determine how subjects are able to control muscle activity and foot endpoint force, independent of neurological injury; and/or test the fMRI scanning protocol and exercises. Because these subjects are contributing to development, we have no a priori expectation of how many will be needed. We guess roughly 20, but we plan to recruit as many as ongoing development needs require (up to 60).

Several studies have shown that recovery of functional and motor capabilities after a stroke is a long process that occurs over several months and even years following a stroke (Takahashi et al., 2005; Ward et al., 2003). Similarly, age is a significant factor that influences recovery. The current protocol is aimed at developing a rehabilitation device and protocol that has the potential to facilitate recovery in patients with lower-limb motor impairments. This is a Pilot study and the results of this study should help us to identify the patients and level of impairment for which this intervention is most optimal. The long-term goal is to apply this therapy to patients at all stages of recovery from stroke. However, we initially restrict ourselves to a subset of patients based on time since stroke onset, to reduce likely statistical scatter in the results. Each patient will serve as their own control in this repeated-measures design (evaluations pre-intervention and post-intervention).

Subject identification and Recruitment

We will recruit subjects following inclusion and exclusion criteria mentioned below.

Patients:

Inclusion criteria:

- Subjects will be stroke patients with persistent moderate unilateral lower extremity deficits, age 50-85 years at time of enrollment.
- Time since stroke will be greater than 6 months (“chronic” stroke survivors).
- Persistent moderate unilateral lower-limb impairment (defined as NIH Stroke Scale – Motor Leg section score of 1-2, to be discussed with the patient verbally during phone screening and assessed by the investigator during the initial

enrollment visit).
- Fluent in spoken and written English

Exclusion criteria:
- Allergy to electrode gel, surgical tape and metals.
- Subjects under treatment for infectious diseases will be excluded from the study.
- Women who are pregnant or planning to become pregnant during the course of the study will be excluded.
- Contraindications for MRI
- Age over 85 years at time of enrollment.

Healthy Controls:
Inclusion criteria:
- Ages 18-85 years
- Non-Stroke Group 1 (“Matched Controls”): 50-85 years old at time of enrollment, to match the population of stroke patients to be studied
- Non-Stroke Group 2 (“Pilot Controls”): 18-50 years old at time of enrollment (Pilot subjects to be initially enrolled early in the design phase of the study, and with enrollment ongoing throughout the study to continue development.)
- No known neurologic, psychiatric or developmental disability.
- Fluent in spoken and written English

Exclusion criteria:
- Allergy to electrode gel, surgical tape, and metals.
- Subjects under treatment for infectious diseases will be excluded from the study.
- Women who are pregnant or planning to become pregnant during the course of the study will be excluded.
- Contraindications for MRI
- Age over 85 years at time of enrollment.

Persons in status relationships with members of the study team may be included in Non-Stroke Group 2 (“Pilot Controls”). Care will be taken to avoid pressuring them to participate. Such steps will include recruitment and guidance in the informed consent process only by study team members who are not in a position of influence over the potential participants.

Recruitment and screening responses from all patients contacted will be recorded in a log for assessment of recruitment yield, to be used in planning recruitment efforts for a later full-scale study. Information to be recorded will include date of contact, eligibility determination, yes/no enrollment, date of enrollment, age, sex, time since last stroke,

and stroke severity. At the conclusion of recruitment efforts for the study, all personal identifying information will be permanently discarded from this log.

Subject Identification:

- Through referrals by the Stroke Neurology team or any clinician involved in patient care, in the in-patient or outpatient setting.
- Clinicians involved in the care of patients may send recruitment letters to eligible patients and ascertain their interest in study participation [email text provided in IRB application].
- Candidates identified for past research in Dr. Prabhakaran's group targeting upper limb therapy may be identified as candidates for this study (if they have lower-limb deficits as well).They will be identified through participant records for protocol #2015-0469 (PI: Justin Williams), which are accessible to Dr. Prabhakaran as a Co-Investigator on that project.
- We also have permission to contact participants who have participated in other research conducted by our group (Prabhakaran 2013-1561). We propose to contact these subjects and ascertain interest in participating as a control subject in this study. Subjects who expressed a written wish not to be contacted for further research (as recorded on their Informed Consent form for protocol - #2013-1561) will be omitted.
- Databases of potential subjects maintained by the UW department of Radiology [Reeder #2012-0303 Volunteer Database] may be used to identify healthy control subjects.
- By posting recruitment flyers (for subject self-identification) at different locations such as the UWHC, the School of Medicine, UW libraries, the University Station Clinic, St. Mary's hospital, Meriter hospital, Madison public libraries, stroke support and other aging support group locations, and on the web pages of Principal Investigator Dr.Adamczyk (http://uwbadgerlab.engr.wisc.edu) and Co-Investigator Dr. Prabhakaran (http://vplab.psychiatry.wisc.edu/).
- Dr. Prabhakaran, who is a radiologist and is involved in clinical imaging protocols of patients, will identify patients who are suitable for study participation as they present to the UWHC, UWMF, WIMR, or Health Emotions Research Institute (HERI) for clinical imaging.

Subject Recruitment:

- Dr. Prabhakaran, who is a radiologist involved in clinical imaging protocols of patients, will recruit patients who are suitable for study participation as they present to the UWHC, UWMF, WIMR, or HERI for clinical imaging or patients who contact him in response to the recruitment flyer. Dr. Prabhakaran or an authorized member of his staff will invite them to participate in the study.

- Candidates identified for past research in Dr. Prabhakaran's group will be identified through participant records for these protocols (Williams 2015-0469 and Prabhakaran 2013-1561). Initial contact will be made by members of the study team of each of those projects. Subjects who expressed a written wish not to be contacted for further research (as recorded on their Informed Consent form for those protocols) will be omitted.
- The study coordinator will be involved in recruiting potential patients referred by the methods above, or patients who contact by telephone or email in response to the recruitment flyer.
- Clinicians involved in the direct care of patients may send recruitment letters to eligible patients and recruit them for the study [recruitment letter attached].
- Recruitment flyers [attached] will be posted at different locations such as the UWHC, the School of medicine, UW libraries, the University Station Clinic, St. Mary's hospital, Meriter hospital, Madison public libraries, stroke support and other aging support group locations, and on the web pages of Principal Investigator Dr. Adamczyk (http://uwbadgerlab.engr.wisc.edu) and Co-Investigator Dr. Prabhakaran's (http://vplab.psychiatry.wisc.edu/).
- Study details will be described to the potential participant by a member of the study team. If the patient expresses willingness to participate in the study, his/her name will be forwarded to the research study coordinator for further follow-up, phone screening, and recruitment according to a screening script [attached in IRB application]. Interested patients may also be asked to directly contact the research study coordinator for further information and screening.
- Participants responding to the recruitment flyer will be contacting the research coordinator. Potential patients will be screened over the phone per the screening script to determine eligibility.
- Healthy volunteers will be recruited through volunteer databases maintained by the Radiology Department (Radiology Volunteer Database, Protocol #2012-0303). Study staff involved with the maintenance of the Radiology Volunteer Database will make initial contact with prospective participants, following procedures established in that protocol. Staff will provide basic study information: the name of the study, the number of visits required, information about the fMRI scan (e.g., it does not involve a contrast agent), and the monetary compensation for participating. For subjects who agree to be contacted further, staff will provide contact information to members of the present study's team who are members of the Radiology Department. This database is available for use as described to all Radiology department faculty, and to our study team through the Radiology appointment of Co-I Dr. Prabhakaran.
- Healthy volunteers may be recruited through flyers posted across the UW campus and downtown Madison.

- Healthy volunteers may be recruited through an email blast to the UW community, through the Division of Information Technology (DoIT). [Sample text of the email is attached.]
- Healthy volunteers may be recruited through word-of-mouth.

Subject Compensation:

- Subjects with stroke will be paid $20 per hour for training sessions, and $25 per hour for fMRI scanning sessions, to compensate for their time and travel expenses.
- Healthy control subjects will be paid $10 per hour for training and $15 per hour for fMRI scanning sessions, to compensate for time and travel expenses.

Privacy and Confidentiality

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

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

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

Study Procedure

Subject Assessments

Behavioral Assessment:

The following commonly used measures of lower extremity motor assessment, standard stroke scales, and measures of activities of daily living will be administered at starting and ending time points to all patients over the length of the study. Healthy normal controls will complete these measures at the beginning of the study. Pilot controls (enrolled before other groups as well as throughout the study for continuing development) will complete a subset as deemed necessary for preparing the study and the study team for the patient and control groups. The assessments are as follows:

1. Six Minute Walk Test (6MWT): The 6MWT is a simple series of laps along a 30 m straight path in a level hallway. Subjects will be instructed to walk as far as they can in six minutes back and forth along this path, according to standard instructions (Rehab Measures - 6 Minute Walk Test). They will be allowed to use mobility aids, to stop or to rest as necessary. Total distance walked will be recorded based on the number of laps (including any fractional last lap), as well as from the IMU motion reconstruction.
2. Timed Up-and-Go test (TUG): The TUG is a simple timed test of how long it takes to stand up, walk 10 feet, turn around, return to the starting point, and sit down. Subjects will be instructed to perform this sequence as quickly as they safely can, using standard instructions (Podsiadlo and Richardson, 1991). The test will be performed in a laboratory or hallway setting.
3. Self-Selected Walking Speed (SSWS): A simple test of the speed a person chooses to walk over a 5-meter distance.
4. Fastest Comfortable Walking Speed (FCWS): A similar test of the “fastest comfortable speed” a person can use to walk over the 5-meter distance
5. Center of Pressure (COP): Center of pressure represents the average location of the vertical force under the feet; its motion is used as an indicator of balance control. Our protocol is a modified version of the ‘Clinical Test of Sensory Interaction and Balance’ (Rehab Measures - Clinical Test of Sensory Interaction and...). COP will be recorded during two 60-second trials of standing as motionlessly as possible on a pressure platform: one with eyes open, the other with eyes closed. During the eyes-open trial, subjects will be instructed to focus their eyes on a spot on the wall a distance in front of them. Metrics of COP control will be computed, including excursion, average velocity, standard deviation, and an estimate of center of mass location (Hof, 2005).
6. Stroke Impact Scale (SIS): The Stroke Impact Scale, or SIS, was created to assess changes in impairments, activities and participation following a stroke will be used in the pre-training and post-training phase of this study. Although the SIS form allows for proxy completion, for this study, subjects will be completing the SIS themselves.
7. Mini-Mental Status Examination (MMSE): The MMSE is a screening tool that

provides a brief, objective measure of cognitive function. We will use the original standard MMSE (Folstein, 1975).

8. Center for Epidemiologic Studies-Depression Scale - Revised (CESD-R): The CESD-R is a self-report scale and includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning.
9. Electromyography (EMG) – is the recording of changes in skin voltage caused by contraction of the underlying muscles. This recording will be obtained using the EMG recording equipment incorporated in the rehabilitation cycle. EMG electrodes will be attached to the surface of the skin over selected muscles of interest in the legs. Muscles may include tibialis anterior, gastrocnemius (medial and lateral), soleus, peroneus longus, peroneus brevis, vastus medialis, vastus lateralis, rectus femoris, iliopsoas, biceps femoris (medial and lateral), semitendinosus, gluteus maximus, gluteus medius, and tensor faciae latae. Proper electrode placement is made according to recommendations from the literature (De Luca, 1997; Rainoldi et al., 2004; SENIAM). A reference electrode will be attached over a bony landmark such as the kneecap, elbow or anterior superior iliac spine (ASIS). Wires will be restrained by tight-fitting clothing, straps or skin-safe tape to prevent motion artifacts. EMG signals will be pre-amplified at the sensor site, and simultaneously recorded by (i) a computer data acquisition system, and (ii) a microcontroller used to control the robotic cycle. Electrodes will be either single-use adhesive electrodes or reusable electrodes. EMG signals will be used as input to the robotic controller as well as for evaluation of outcomes.
10. Leg strength: will be assessed using isometric contractions against the instrumented pedals of the rehabilitation cycle.
11. Health Questionnaire: to document the general physical health and social habits of all subjects.
12. Pain Scale: Patients will be asked to rate their degree of pain on a scale of 0 (no pain) to 5 (in tears).
13. Modified Ashworth Scale: will be used to assess muscle tone in each hip and knee.
14. Fugl Meyer Assessment (FMA): range of motion testing of lower and upper limb capacity. The lower-limb section of the 37-item FMA (11 items) (Hsieh et al., 2007) will be used to categorize stroke severity at the time of block randomization into one group or another. If time allows, the complete 37-item FMA will be performed instead for completeness.
15. Pre and post intervention questionnaire – a series of questions to get a sense of the patient's expectations, and general tiredness and motivation levels at the beginning and end of the study, and at the start of intervention each day. The questionnaire administered at the beginning of the study will also ask questions regarding any allergies the patient may have and his/her experience with

pedaling exercise. The post-intervention questionnaire is to get the patient's feedback regarding their experience in the study.

Gait Assessment

- During the locomotion tests only, inertial measurement units (IMUs) will be attached to the shoes, waist and one or both arms of the subject, using soft straps with Velcro closures. The IMUs to be used may be wired or wireless; if wired, the cables will be restrained inside clothing or with straps. The sensors will log acceleration, angular velocity, magnetic field, and altitude data while the subject walks in the hallway (6MWT) or on a short circuit starting from a seated position (TUG) or a standing position (SSWS, FCWS). Data from these sensors will be used to assess stride length, speed, foot placement variability, symmetry, and gait stability.

Functional MRI scans:

- Participants who will undergo an MRI scan will be screened for MRI eligibility using the UW Department of Radiology's standard clinical MRI screening form.
- All patients in the study will be scanned at two time points (before and after intervention).
- Healthy Normals in the Typical Comparison group will be scanned once.
- Healthy Normals in the Pilot group will not be scanned.

Training on the robotic rehabilitation cycle:

- Patients assigned to the "robotic" and "control" groups will receive training following the procedure outlined below; these patients will complete 12 training sessions over one month.
- Healthy normal subjects will receive modified training on the device up to five (5) times.

Robotic Training Group (Robotic Group): Procedure

Robotic therapy protocol description:

The "Robotic" group will be trained using a robotic training protocol, designed to incentivize recovery of volitional motor control by dynamically changing task demands throughout the training period. One or more target tasks will be chosen to incentivize motor activity mimicking different sub-functions of gait, including some which are not normally excited in typical cycling behavior. Candidate tasks include: leg swing-through (hip flexion with knee extension near the most proximal pedal position); leg retraction (hip extension with knee flexion near the distal pedal position); leg extension (hip and knee extension – the power stroke of normal pedaling); leg retraction (hip and knee

flexion –the passive recovery stroke in normal pedaling); step-like loading (hip and knee extension while bike pedals backward through proximal pedal position, then hip and knee flexion through the distal position); and a “foot placement-like” task (alternating medial and lateral force) during normal pedaling. Also, tasks may be designed to target non-gait motions such as hip ab/adduction. The required task may be changed periodically, to incentivize attention to task and cortical control, rather than short-term adaptation (e.g. cerebellar).

A user display screen will indicate the desired task at all times, and indicate measures of asymmetry and performance. Performance will be defined as “task matching performance,” computed as the normalized projection of the vector-valued foot force or EMG signal (all channels) onto the specified task vector. Using this metric, 1.0 indicates perfect task matching; zero (0.0) indicates no force/EMG signal in the direction of the specified task; negative values indicate force production opposed to the specified task (impossible for EMG), and values greater than 1.0 indicate excess force or EMG activity in the specified pattern. We will also explore other methods for reducing multidimensional data to informative summary measures. Performance will be displayed to the user on a computer screen using a “speedometer” or similar graphical display, and will be incorporated into the control system of the robotic cycle and recorded for later analysis. Alternative measures of performance may also be used.

The controller will reward good performance with increased crank speed, and will penalize errant coordination with decreased crank speed. The subject’s explicit goal will be to maintain a constant speed; this will only be achievable through proper motor control. Errors in either direction (too high/too low) will result in a crank speed error, representing imperfect performance. As subjects gain skill in the task, task difficulty will be increased by increasing the target signal magnitude of the specified task. This specific task is one among many possible therapy designs, which this Pilot study is intended, in part, to choose among. The specific reward structure and task definitions may be modified based on tests with healthy controls as well as early patients, in order to optimize the therapy delivered. All forms of task will involve only seated pedaling motions. Possible other tasks include (but are not limited to): pedaling that emulates a typical bike or exercise bike; tasks that change resistance torque instead of crank speed as a reward; tasks that reward forces opposing the motion of the pedals; and tasks that use a variety of different calculations to determine the “task matching performance” metric.

This therapy protocol will occupy 30 minutes of each training session. Prior to testing, EMG electrodes will be placed on the major muscles of both legs, a procedure that takes roughly 15 minutes. Another 15 minutes is allotted for changing clothes, briefing

and debriefing the subject, and other ancillary study activities. The total time allotted per training session is 1 hour.

fMRI Scanning Protocol description:

fMRI scans will be used to measure task-specific cortical activity in sensorimotor areas as outlined in the *data processing* section. Due to uncertainty about available testing equipment, one of two protocols may be used for fMRI testing: physical stepping with an MRI-compatible stepping machine (Ergospect GmbH; Forouzan et al., 2014), available at UW-Madison through Dr. Oliver Wieben; or imagined/visualized cycling. The preferred activity is actual stepping with a passive MRI- compatible stepper. Imagined/visualized cycling is proposed as a suitable substitute activity within the constraints of the fMRI environment if for some reason the stepping machines cannot be used.

If the MRI-compatible equipment is available for this study, each subject will recline and position his head within the MRI bore, while his feet are clipped to the pedals. The torso will be stabilized with straps to minimize motion artifacts affecting the scan. During the scan, the subject will be instructed to step at a constant speed, while fMRI scans incrementally identify the activity in different portions of the brain. This protocol will best match the context of the fMRI scan to that of the training task.

If the MRI-compatible equipment is determined to be unsuitable for this study, each subject will recline and position his head within the MRI bore, with the body relaxed and stationary.During scanning, the subject will be instructed to imagine consistently performing the cycling task used in training. While not strictly equivalent to the real task, an imagined task (motor imagery) has been shown to evoke neural activity much as real tasks do (Pfurtscheller and Neuper, 1997; Porro et al., 1996; Sharma et al., 2006). Changes in such activity during imagined tasks will suggest that neural reorganization occurred.

Summary of study visits/procedures: <u>Robotic group</u>

Subjects assigned to the Robotic group will complete the following study visits. Note the timeline and schedule of visits given below is only representative; for example, conditions beyond the control of the study group and patient –related factors may lead to fewer number of visits per week and not all study events may be completed during one visit. We will seek to maintain a constant number of 12 training visits for all stroke subjects. Subjects who drop out before this number may be replaced at the discretion of the PI.

Timeline:

- **Timepoint 1 Visit** – will include baseline behavioral assessments, gait tests,

written questionnaires, and fMRI scan

- Training session #1 : [this could occur on the same day as the first behavioral and fMRIsessions]
- Visit 2 – training session #2
- Visit 3 – training session #3
- Visit 4 – training session #4
- Visit 5 – training session #5
- Visit 6 – training session #6
- Visit 7 – training session #7
- Visit 8 – training session #8
- Visit 9 – training session #9
- Visit 10 – training session #10
- Visit 11 – training session #11
- Visit 12 – training session #12
- **Timepoint 2 Visit** – will include endpoint behavioral assessments, gait tests, written questionnaires, and fMRI scan 2 at the end of the intervention . This visit could occur on the same day as the final intervention, or the next day or two per subject and experimenter convenience.–

Each behavioral session will take roughly 1 hour. Each intervention session will take about 1 hour. Each fMRI scan session will take 2 hours. The behavioral and fMRI sessions will take place at WIMR; the training sessions will take place at the UW-Madison Mechanical Engineering Building. We will arrange and pay for transportation between sites as needed.

Evidence suggests that targeted lower limb cycle training can improve walking distance and speed in stroke patients. Some example studies used a program of 10-15 training sessions over 2-3 weeks (Brown et al., 2005; Katz-Leurer et al., 2006), and 12 sessions over 4 weeks have been used in robotic gait training (Krishnan et al., 2013). This basis suggests that the intended duration and intensity of training (12 sessions of 30 minutes over 4 weeks) will be sufficient to demonstrate improvements in gait and motor function if they occur. However, this protocol is a target, which may be adjusted for individual patients as necessary to accommodate schedules and other needs. In such cases, the goal will be to keep the total number of training sessions constant for all patients. However, if interim results [after 6-10 patients] suggest that 12 sessions is not sufficient, then the study team will make provisions to increase the number of study sessions. Finally, if it appears that the subject will take more than 15 sessions to complete the study, then subject participation in the study will end.

Aerobic Training Group (Control Group): Procedure

Patients in the Control group will perform an identical protocol to that used by the Robotic group, except that the robotically-incentivized pedaling exercise will be replaced with an aerobic therapy program. This intervention will emulate an established form of motorized pedaling therapy similar to that used in commercial motorized exercise bikes to improve underlying cardiovascular unfitness contributions to gait impairment. This therapy implements a simple version of assist-as-needed and constant-velocity control. The patient's target pedaling speed (e.g. 20 rev/min (to be finalized through pilot tests: range 15-50 rev/min) and power level (set by heart rate to require approximately 50-70% of maximal oxygen uptake, estimated individually for each patient) are set at the beginning of each session and a motor provides assistance or resistance to compensate for the performance of the patient. The exercise will be performed in this mode for 30 minutes per training session.

Healthy Normal Controls

Non-Stroke Group 1 (Typical Comparison Group): Procedure

Healthy Normal subjects in this group will be administered the same behavioral measures as the Stroke groups, and 1 fMRI scan while stepping (or imagining stepping) at the beginning of the study. Subjects will then undergo up to 5 training sessions on the robotic cycle with a modified training task. This task will incentivize performance of a novel motor task, such as eccentric force control, mediolateral force control, or EMG coordination in a pattern different from normal cycling. Performance in matching the target task will be evaluated across the training sessions.

Non-Stroke Group 2 (Pilot Group): Procedure

Healthy Pilot subjects will test the therapeutic tasks as they are designed, as well as a subset of the assessments (e.g. IMU gait data collections). The subjects will provide user feedback on the design of each task, and their data will provide insight into the pattern and time-course of motor learning in healthy subjects.

Images and Audio/Video Recording

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

- in lab meetings to discuss the subject's progress and possible ways to improve testing
- to assess inter-tester reliability and for training new personnel before they

administer the behavioral tests
- in research group presentations with collaborators or at conferences to show examples of subjects performing the tasks in this research study
- in publications to illustrate the protocols used in the study.

When possible, photographs and video recordings will be done such that the subject will not be easily identifiable. Identifiable features in images will be electronically obscured before publication.

Subject randomization:

Subjects with stroke will be randomly assigned to the intervention [robotic] or non-intervention [aerobic/control group]. Randomization will be done using a block design. We will control for sex (male vs female) and stroke severity (based on Fugl Meyer assessment) to ensure comparability across groups.

Data and Safety Monitoring Plan

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

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

All researchers and research staff involved in the study have completed Human Subjects and HIPAA training and will be continuously involved in data and safety monitoring. Data and safety monitoring will occur on a continuous basis. fMRI and EMG data will be reviewed by the PI, Co-I and a group of study team members on a continuous basis. All behavioral measures will be reviewed by the study team within two weeks of collection.

Data Processing/Data Analysis

Behavioral Data:

For the analysis of pre- and post- measures on the behavioral data, we will perform repeated measures ANOVA tests with time as the independent variable and score on

each behavioral test as the dependent variable.

In order to assess the overall effect of the rehabilitation protocol, we will perform multiple regression analyses to determine the extent to which data from each modality explains the proportion of the variance in the behavioral outcomes. The dependent variable is the score on the behavioral test and the predictors are the task tracking performance (error) in EMG and foot force during the last training session, and the percent signal change in targeted brain areas from the fMRI data.

In addition, we will also perform a multivariate ANOVA to examine the mixed model with Time of testing (pre, post) as a within subject factor, Group (robotic therapy, aerobic therapy) as the between-subject factor, and dependent variables of percent signal change from the fMRI data and each of the behavioral scores. This will help us to determine if there is a significant difference between the groups in terms of behavioral performance and functional activations and also to determine whether these dependent measures change over time.

fMRI data:

SPM5 (Wellcome Department of Cognitive Neurology, London, UK) will be employed for motion correction and used to normalize the EPI BOLD images to a standard space using a 12 parameter linear transformation. The images will be then spatially smoothed using an 8.0 mm Gaussian kernel. Finally, the statistical package contained within SPM5 will be used to estimate the effects of condition at each voxel according to the general linear model. The analysis will be entered into SPM5 as an epoch design of the fixed response/box car form convolved with canonical HRF, reflecting the appropriate activation and rest periods within the total scanning period. Images will be high-pass filtered at 128 s to remove low- frequency drifts in blood oxygen level-dependent signal.

Percent signal change (after vs. before) will be compared statistically between the two groups using unpaired two-sample t-tests between the robotic and aerobic groups. A repeated measures ANOVA will be performed with the dependent variable being the percent signal change and between subjects factor Group (robotic therapy, aerobic therapy), and within subject factor Time (before and after training).

Along with percent signal change over time, we will also compute region-wise laterality index. ROIs will be predefined in each hemisphere. For each ROI, laterality index (LI) will be defined as: Number of activated voxels in the affected hemisphere / [voxels in the left hemisphere + voxels in the right],thus giving LI for each ROI. LI = 0.5 indicates symmetrical activation; LI< 0.5 indicates an activation deficit on the affected side, and LI > 0.5 indicates increased activation of the affected side. This index will provide a way of

understanding the contribution of each brain area (ROI) to the overall task-related activation in one session and changes in laterality over time. The percent signal change and LI are purely quantitative measures, in order to ensure that change in plasticity over time is captured adequately and does not rely on individual fMRI reader's abilities to gauge these changes simply on the basis of a "visual read" of the fMRI scans.

fMRI data is in the form of many voxels that are traditionally analyzed separately. This analysis needs to be corrected for the thousands of statistical tests performed. Corrections need to consider the spatial nature of fMRI data so simple schemes, such as the Bonferroni correction, are not appropriate. A method that controls the family-wise error (FWE) balances the statistical threshold with a minimum cluster size to produce an overall p-value for an activation cluster (Forman et al. 1995). We will use this FWE technique to correct our functional data for multiple comparisons.

Data from Healthy Normals:

The EMG data from healthy normals will help us to determine if the subjects are able to learn novel motor tasks that decompose traditionally synergistic muscle groups during cycling, and whether they show any handedness bias. The fMRI data from normals will show traditional areas of activation while performing or imagining a motor task; the average map derived from these subjects will serve as a control for the patients.

Sample Size

Below we give sample size calculations based on the gait outcome measures (six-minute walk test (6MWT), self-selected walking speed (SSWS) and fastest comfortable walking speed (FCWS)), as well as the expected changes in brain activations:

The sample size required per group is computed using the following formula: N (per group) = 2* ((z(1-α/2) + z(β))*σ/d)^2,
where ***d*** is the expected difference in outcome value, post- vs. pre-training; ***σ*** is the estimated standard deviation; ***α*** is the alpha error we would like to control; and ***β*** is the statistical power. Here we set a statistical goal of 80% power (***β*** =0.80, z(***β***)=0.84) and ***α*** level 0.05 (z(1- ***α*** /2) = 1.96).

Based on a recent study of locomotor rehabilitation in chronic stroke (Bowden et al., 2013), we expect: a difference in 6MWT of 154.3 +/- 171.1 meters; a difference in SSWS of 0.21 +/- 0.13 m/s; and a difference in FCWS of 0.18 +/- 0.15 m/s. These give sample size estimates of 20, 6 and 11 subjects, respectively. This sample-size estimate is conservative, using a two-tailed test when in fact we expect to test explicitly for an

increase (one-tailed test). For a one-tailed distribution (using z(1- α) = 1.65), sample size estimates are 16, 5 and 9 subjects.

For fMRI signal changes at the single voxel level, we expect to achieve statistical power of 80% with a significance cutoff of alpha = 0.05 using a sample size of 12 subjects, as reported in literature (Desmond and Glover, 2002).

The maximum of all sample size estimates for two-tailed tests is 20 subjects. However, the outlier is the 6MWT; without this, the maximum would be 12 subjects. Balancing the practical (budgetary, time) need for a small sample with the need to capture as many metrics as possible, **we choose a sample size of 16**. This sample size just captures the expected change in 6MWT (in a one-tailed test) and is well above the necessary sample size for other outcomes. Based on previous experience, we estimate a 20% dropout rate (due to patients not being able to complete all sessions, or not coming back for post training evaluation). We therefore propose to enroll 20 patients per group (robotic, aerobic), for a total of 40 patients.

Up to 20 healthy controls will be enrolled to form a normal data set of similar size to each patient group.

Up to 60 additional healthy subjects will be enrolled for pilot testing. Pilot subjects are not a statistical group, so no specific sample size is required.

Potential Risks and Benefits

Cycling

Recumbent cycling at moderate intensity is widely considered a safe activity. Nevertheless, common risks associated with exercise may also occur in this study. These risks include muscle soreness, joint soreness, a feeling of exertion, and being out-of-breath. Robotic control of the cycle means that limbs may be driven through passive movements, and may be driven opposite to the forces generated by the user, which may increase muscle soreness. As with any device, there is a slight risk of malfunction; the cycle is equipped with emergency stops on the handles that suspend operation of the motor in this event.

EMG (electromyography):

EMG is a diagnostic tool that evaluates muscle or nerve problems. It uses surface electrodes to assess the activity of muscles and the ability of motor neurons to control the muscular system. Risks associated with this procedure are minor and may include skin irritation and general soreness in the areas being tested. This may last for a few days and can be relieved with an over-the-counter pain reliever.

Heart Rate Monitoring:
A standard heart rate monitor will be strapped around each subject's chest. Risks associated with this measurement are minor, and include discomfort due to the strap and monitor module.

Disease Transmission:
Because the same rehabilitation cycle equipment will be used by multiple subjects, there is potential for disease transmission. This risk is reduced to an extremely small level by two mechanisms. Subjects reporting treatment for infectious disease will not be allowed to participate. Secondly, equipment surfaces with which subjects come in contact will be disinfected following each subject's use of the equipment.

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

Within this context, there are still several potential hazards associated with a typical MRI scan. Subjects who will undergo an fMRI scan will be screened for MRI eligibility using the UW Department of Radiology's standard clinical MRI screening form, once during the phone screening and again immediately before each fMRI scan. Subjects will be excluded as necessary to minimize risk associated with possible MRI hazards including the following:

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

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

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

MRI:

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

Minimizing risks:

Subjects are under supervision at all times during the experiments and will easily be able to communicate any discomfort. Equipment will be disinfected after every subject. The robotic cycle will be equipped with emergency-stop switches on the handle grips, which will disable the motor's power amplifier when released, bringing the machine to a stop.

To minimize risks in moving around the buildings, participants will be allowed to use any mobility aids (canes, walkers, wheelchairs, etc.) anytime they are standing or walking. Participants will be helped into and out of the seat on the robotic cycle by the project staff. For moving throughout the building, elevators and ramps are available. The exercise itself is a recumbent (seated) cycling exercise; the cycle will be equipped with a seatbelt that will be kept fastened during testing and training.

Medical emergencies:

We have an MD on call, Dr. Prabhakaran, who will be available to respond and attend to any medical emergency during the course of a study session. In addition, we will contact 911 in the event of an emergency.

Emotional Health of Subjects

The CESD-R Assessment used in this study asks about symptoms of emotional distress such as depression. We will evaluate the results of this assessment on the same day it is taken. Written answers from subjects will be entered by an experimenter into the anonymous online version at http://cesd-r.com. The result reported by the system will be used to determine the subject's status relative to indicators of a major depressive episode (according to the criteria at http://cesd-r.com/cesdr/). If major depressive episode is indicated as "possible," "probable," or "meets criteria," we will follow-up with the following actions:

- We will inform the subject that the assessment shows that (s)he may be having an episode of major depression, along with the severity/certainty rating reported by the CESD-R criteria.
- We will inform the subject that if (s)he is experiencing emotional distress, (s)he should contact his/her physician or other health care provider, such as a mental health professional.
- We will call 911 if the subject appears to be in immediate danger of harming himself/herself.
- We will give the subject the option of withdrawing from the study if (s)he desires.

No action will be taken if the CESD-R result indicates "subthreshold symptoms" or "no clinical significance."

Benefits

No immediate benefits are expected for subjects involved in the study. It is possible that subjects may experience some improvement in lower limb function or cardiovascular health. There are significant potential scientific benefits in the translation of new therapeutic technologies from concept to patient care.

Data and Record Keeping

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

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