Protocol

1. Project Title

Rehabilitation of corticospinal control of walking following stroke: ABCs of Walking

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3. Abstract:

Current approaches for rehabilitation of walking following stroke do not sufficiently restore mobility function. For instance, fewer than 50% of individuals with stroke-induced walking dysfunction recover the ability to walk independently in the community. New breakthroughs in rehabilitation are needed that will target the motor impairments responsible for poor walking function in individuals post-stroke. Functional recovery can occur in response to task-specific neuroplasticity of damaged brain circuitry. The corticospinal tract is an important target for neuroplasticity because it plays an important role for control of walking in humans. We and others have shown that, compared to steady state walking, accurate gait modification (ACC) tasks are a potent behavioral stimulus for activating the corticospinal tract. Therefore, we propose that training with ACC tasks (e.g., obstacle crossing/avoidance, accurate foot placement, etc.) may be superior to training with steady state walking (SS) for eliciting corticospinal neuroplasticity and recovery of walking function. Most rehabilitation paradigms have previously focused on SS training. This is largely because therapists consider it premature to progress to ACC tasks when persistent deficits of steady state walking still remain. However, this reasoning might be counter-productive, because training only steady state walking may not sufficiently stimulate neuro-plasticity of the damaged corticospinal pathway. In contrast, ACC training is specifically designed to stimulate corticospinal neuroplasticity. Importantly, since ACC training targets a central mechanism, its benefits are expected to generalize across walking conditions. Furthermore, it is expected to benefit most stroke survivors who possess at least a minimal residual capability to activate the corticospinal tract. ACC training also provides an opportunity to practice tasks that are analogous to challenges encountered in the home and community environments. Accordingly, there is strong mechanistic and practical rationale for ACC training.

A number of earlier studies including our own pilot training intervention have cumulatively established exciting preliminary evidence showing that walking function is enhanced by training with ACC tasks. However, no prior study has been specifically designed and sufficiently powered to determine the extent to which the “accurate gait modification” ingredient is crucial for recovery of walking function. Also not known is the extent to which ACC training reduces the neural impairments underlying poor walking function. The central hypothesis of this study is that ACC training will be superior to SS training for increasing walking function and for reducing underlying neural control of the paretic leg in adults with post-stroke hemiparesis. Each intervention will involve twelve weeks of training, 3 days per week (36 sessions total), and will emphasize the motor learning principles of high intensity, repetition and task-specificity.

Assessments will be conducted immediately pre-intervention, immediately post-intervention and at a follow-up session 3 months later. Walking function will be measured in the lab and in the "real world". Neural impairment measures will include electromyography-based measures of inter-muscular coordination and corticospinal drive.
We expect that the benefits of ACC training will justify larger randomized controlled trials to optimize the use of ACC training, including timing relative to stroke, combination with other therapeutic approaches, and identifying individuals who are most likely to benefit from this approach. This research is expected to enhance walking function in stroke survivors, including for the 15,000 Veterans who suffer a stroke each year.

4. Background:

The Veterans Health Administration (VHA) estimates that each year over 15,000 Veterans are hospitalized for stroke. Stroke is the leading cause of serious long term disability in the United States. Approximately 600,000 individuals incur a stroke each year, with one quarter of those occurring in adults under age 65. The proportion of survivors among all age groups has increased in recent years due to improved acute medical care. This has resulted in a large cohort of survivors whose objectives are to resume their societal roles, including employment, leisure, and social activities. One of the most common goals in persons with post-stroke hemiparesis is to improve walking function and independence. Indeed, 93% of stroke survivors rate their ability to "get out and about" as being important or essential. It is therefore striking that less than 50% of stroke survivors regain the ability to walk in the community, limiting participation in a broad range of activities including employment, leisure, and social activities. Restoration of walking function is not sufficiently achieved by current rehabilitation approaches. The proposed project is important and significant because it may yield a breakthrough in restoration of walking function for stroke survivors.

Walking is a complex sensorimotor task requiring coordinated activation of numerous muscles. The basic reciprocal pattern of walking is facilitated by pattern generating circuits in the spinal cord. For typical steady state walking, these circuits are activated by an indirect locomotor pathway believed to include the motor cortex, basal ganglia and brainstem locomotor centers as well as by signals from the cerebellum and the periphery (e.g., sensorimotor reflexes). Also important to walking is the corticospinal tract, which is a direct pathway connecting the cerebral motor cortex to lower motor neurons. Recent evidence confirms an important link between functional/structural integrity of the corticospinal tract and recovery of walking ability after stroke. The corticospinal tract is believed to contribute to a variety of motor processes, including selective control of muscle activation and movement, modulation of spinal reflex sensitivity, and acquisition of new motor skills. And it is now clear that the corticospinal tract contributes to muscle activation during steady state walking throughout the gait cycle in humans, as evidenced by studies using electroencephalography, imaging and transcranial magnetic stimulation.

The primary cause of hemiparesis following stroke is damage to the motor cortex, cerebral white matter and/or posterior limb of the internal capsule, all of which contribute to the corticospinal pathway. Given the important of the corticospinal pathway to control of walking, it is crucial to engage this damaged tissue during rehabilitation. Compared to

steady state walking, walking tasks that involve accurate foot placement and/or gait modifications are known to require much stronger corticospinal activation. Accordingly, we propose that accurate gait modification tasks (ACC tasks) are a highly potent behavioral stimulus for activity-dependent plasticity of the corticospinal tract. This leads to an urgent question: Will an intervention that provides a more potent dose of corticospinal activation during walking, such as ACC training, yield even larger functional benefits than standard rehabilitation that uses steady state walking?

5. Specific Aims:

Specific Aim 1: Determine if ACC training is superior to SS training for improving walking function.
Hyp. 1a-1d: ACC training will yield significantly larger improvements in walking function, as evidenced by: a) preferred walking speed; b) walking speed during obstacle crossing; c) total daily step activity; d) frequency of community ambulation.

Specific Aim 2: Determine if ACC training is superior to SS training for improving neural control of walking.
Hyp. 2a: ACC will yield significantly larger improvements in inter-muscular coordination, as indicated by the characteristics of EMG inter-muscular coordination patterns.
Hyp. 2b: ACC will yield significantly larger improvements in corticospinal drive during walking, as indicated by EMG synchrony in leg muscles.

6. Research Plan:

6.1. Recruitment and Screening
We will recruit 64 participants with chronic post-stroke hemiparesis (6-48 months post-stroke) to take part in rehabilitation of walking according to the following list of inclusion/exclusion criteria. The Principal Investigator reserves the right to enroll participants who exhibit minor deviations from these criteria.

Inclusion criteria

- occurrence of a single unilateral stroke within the previous 6-48 months (verified by MRI or CT from medical record)
- living in the community and able to travel to training and assessment sites
- approval of participation by primary care physician
- age 18 - 80 years
- lower extremity paresis indicated by Fugl-Meyer Assessment Score < 30 deficit in at least one “synergy” subcategory (II – IV) of the Fugl-Meyer Assessment
- self-selected 10m gait speed of 0.4 – 0.8 m/s (with or without an ankle/foot orthosis or cane)
- able to provide informed consent
- willingness to be randomized to either intervention group

Exclusion criteria

- neurological disorder or injury (other than stroke) such as Parkinson' s disease or spinal cord injury
- severe arthritis, such as awaiting joint replacement, that would interfere with study participation
- cardiovascular disease (congestive heart failure, significant valvular disease, history of cardiac arrest, presence of an implantable defibrillator, uncontrolled angina)
- myocardial infarction or major heart surgery in the previous year
- cancer requiring treatment in the past three years, except for nonmelanoma skin cancers and other cancers having an excellent prognosis (e.g., early stage breast or prostate cancer)
- lung disease requiring use of corticosteroids or supplemental oxygen
- renal disease requiring dialysis
- current diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder
- Mini-Mental State Examination (MMSE) score <23
- significant depression (e.g., Patient Health Questionnaire score > 14)
- severe obesity (body mass index > 40)
- uncontrolled hypertension (systolic > 200 mmHg and/or diastolic > 110 mmHg)
- uncontrolled diabetes with recent diabetic coma or frequent hypoglycemia
- bone fracture or joint replacement in the previous six months
- diagnosis of a terminal illness
- current participation in physical therapy or cardiopulmonary rehabilitation
- significant visual impairment affecting capability to gauge movement accuracy
- previous enrollment in a clinical trial for recovery of walking function
- current enrollment in any clinical trial
- planning to relocate out of the greater Gainesville FL area during the study period
- unable to communicate sufficiently with study personnel
- clinical judgment regarding safety or noncompliance

We will use a multi-pronged approach for recruitment, including:

- Posting of flyers: Flyers advertising the study will be posted throughout the Malcom Randall VA Medical Center, Brooks Rehabilitation Hospital, and the Jacksonville VA Clinic.
- Newspaper advertisements: We will run advertisements in regional and local newspapers in the Gainesville and Jacksonville areas. Advertisements will be designed to target Veteran enrollment.
- Research Registries: The VA Brain Rehabilitation Research Center and the Brooks Clinical Research Center maintain IRB-approved registries of individuals who have experienced a neurological injury and who are interested in participating in research trials. The registries will be queried for individuals post-stroke who have difficulty walking and who meet other specific criteria for this study.
- Community Outreach: The VA Brain Rehabilitation Research Center and the Brooks Clinical Research Center each participate in approximately 4 community events per year. This includes VA Health Fairs, which is a good opportunity to

target Veteran enrollment. Flyers and post-cards will be distributed at these events.

- Internet: The Brooks Clinical Research Center maintains a website dedicated to providing patients with information about the research being conducted (http://www.brookshealth.org/why-brooks/rehabresearch).
- Inpatient Stroke Care: Each individual admitted to Brooks Rehabilitation is asked to sign a HIPAA Authorization to be contacted with information about research opportunities. Each person who provides authorization will be contacted to participate in the Brooks Research Registry.
- Outpatient and Home Care: Brooks Clinical Research Center will recruit from the outpatient rehabilitation clinic and from Brooks Home Care Advantage Health Agency by providing research information postcards in each admissions packet. Home Care stroke admissions are approximately 180 per year. Outpatient clinics will have post cards and fliers in all 27 clinics. All post card inquiries will be followed up by the phone screening and consent to the registry.

6.2 Preliminary screening of potential participants

Volunteers who are interested in participating will be screened by telephone using an IRB approved script. Those who pass the phone screen will be sent a form entitled "Authorization for disclosure of health information/patient request for access to patient health information". This form will allow us to contact the volunteer's medical provider(s) in order to obtain information about the volunteer's stroke and other medical information related to this study. This information is being used for screening purposes to ensure that volunteers meet eligibility requirements. The volunteer's physician will also be asked to provide confirmation in writing that the volunteer is medically approved to participate in the rehabilitation intervention.

6.3 Enrollment and on-site screening

Volunteers who pass the preliminary screening will be invited to attend an on-site screening session. Upon arrival, the individual will be consented for participation in on-site screening only. Assessments will include the Fugl-Meyer Assessment, walking speed, Mini-Mental State Exam, Patient Health Questionnaire, pain questionnaire, body mass index and blood pressure. Criteria are listed above in Section 6.1. Other clinical assessments/questionnaires may also be conducted including the Functional Independence Measure, Dynamic Gait Index, Environmental analysis of mobility questionnaire, Activities Specific Balance Confidence Scale, Satisfaction with mobility function and recovery (walking items from the Mobility and Self-Care (MOSES) Questionnaire) and clinical assessment of peripheral somatosensation.

6.4. Assessments

Participants who pass the on-site screening will invited to return to our research site for full enrollment in the rehabilitation trial and for baseline assessment. At each time point of the study (baseline, post-intervention and follow-up), participants will undergo a battery of assessments. A physical therapist will perform all clinical assessments. The therapist performing the assessments will be blinded to group assignment. At the discretion of the Principal Investigator, any assessment listed here may also be performed during the

rehabilitation sessions in order to monitor the progress of rehabilitation and/or to address secondary research questions of interest.

Primary Assessments

Specific Aim 1a: Preferred overground steady state walking speed
Methodology and Instrumentation: Participants will walk overground over a GAITRite instrumented walkway (CIR Systems Inc, Havertown, PA), which calculates walking speed.
Protocol: Participants will begin walking 3 meters before the start of the walkway and continue to walk 3 meters after the end of the walking, in order to avoid acceleration and deceleration at each end of the walkway. Walking speed will be recorded three times at each assessment.
Analysis: The median walking speed measured at each assessment will be used for subsequent analysis. An intent-to-treat analysis will be conducted to test the primary hypothesis using regression analysis, with the change of walking speed as dependent variable, the training group as independent variable, and accounting for covariates including baseline walking speed, severity of stroke (Fugl-Myer Assessment), co-morbid conditions (Charlson Index), and physical activity level (CHAMPS Questionnaire).

Specific Aim 1b: Walking speed during obstacle crossing
Methodology and Instrumentation: Participants will walk overground across a 20 foot course that has two obstacles (1” x 3” x 36” dimensions) placed at 6 and 14 feet into the course, as previously conducted by Shumway-Cook and colleagues. Time will be recorded using a stop watch, and speed calculated according to the known time and distance.
Protocol: Participants will begin walking 3 meters before the start of the walkway and continue to walk 3 meters after the end of the walking, in order to avoid acceleration and deceleration at each end of the course. Walking speed will be recorded three times at each assessment.
Analysis: The median walking speed measured at each assessment will be used for subsequent analysis. The change between pre-training and post-training (or follow-up) will be calculated. Between-groups difference of the change value will be assessed using a regression analysis similar to Aim 1a.

Specific Aim 1c: Total daily step activity
Methodology and Instrumentation: Step activity will be measure over a three-day interval using a Step Activity Monitor (SAM) that is worn at the lateral malleolus of the non-paretic leg. The device is safe, highly accurate, unobtrusive for the wearer, capable of continuously recording data in short time intervals, and capable of withstanding daily home and community use. Proper use of the device will be demonstrated to each subject at each assessment time point. Follow-up phone calls by study staff will be made during the 3-day intervals to enhance compliance and respond to any problems.
Protocol: The following instructions will be provided to each participant: When you wake up in the morning, place the SAM on the outside of your less involved ankle. Make sure the arrow on the monitor is pointing upward. Go about your daily activities. You do not need to “pay attention” to it throughout the day. You will not want to get the monitor wet,

so take if off for bathing, showering, and/or swimming. Remove the SAM while you are sleeping at night, and put it back on in the morning. If you forget to put it on, call us and we will give you instructions about what to do.
Analysis: The average daily step activity will be calculated across the three day interval. The change between pre-training and post-training (or follow-up) will be calculated. Between-groups difference of the change value will be assessed using a regression analysis similar to Aim 1a.

Specific Aim 1d: Walking activity in the community
Methodology: As previously conducted by Shumway-Cook and colleagues, participants will maintain a written log of trips taken away from home (i.e., into the community) and the number of walking-related activities performed on each trip.
Protocol: Participants will complete the trip activity log for a one week interval at each assessment time point. Participants will be contacted by telephone in the middle of the week and end of the week to obtain results and for additional interviewing to ensure maximal accuracy of reporting.
Analysis: The primary outcome will be the ratio of [total walking activities / total trips away from home] during the one week recording interval. The change between pre- and post-training (or follow-up) will be calculated. Between-groups difference of the change value will be assessed using an analysis similar to Aim 1a.

Specific Aim 2a: Inter-muscular coordination
Methodology and Instrumentation: We will use the inter-muscular coordination measurement approach described in:
Clark DJ, Ting LH, Zajac FE, Neptune RR and Kautz SA. Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke. *J Neurophys,* 103(2): 844-57, 2010.
Surface EMG will be recorded from tibialis anterior (TA), soleus (SO), medial gastrocnemius (MG), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), lateral hamstrings (LH) and gluteus medius (GM) of both legs. Each skin site will be shaved and firmly rubbed with a sterile alcohol wipe prior to electrode placement. EMG signals will be detected by disposable surface gel electrodes placed on the skin over the muscles of interest.

Protocol: Participants will walk at preferred steady state speed on the treadmill and overground. After participants are given ample opportunity to get familiarized with treadmill walking, we will record EMG during three 30-second bouts of walking. We will conduct ten 10-meter bouts of overground walking in order to provide sufficient data for analysis.

Analysis: Data from treadmill and overground assessments will be analyzed separately. Data will be analyzed using custom data analysis programs created in Matlab (The Mathworks, Natick, MA), which have developed and implemented for our earlier research studies. The number of independent inter-muscular coordination patterns for each leg will be calculated using a non-negative matrix factorization (NNMF) algorithm. EMG from all eight recorded muscles of the paretic leg will be corrected for baseline offset (de-biased), rectified, and smoothed (4 Hz lowpass). The EMG data will be combined into an m x t

matrix, where m= # of muscles and t=time. This matrix will be entered into the NNMF algorithm, which extracts a smaller set of factors (i.e., inter-muscular coordination patterns, or ICPs) that identify the underlying common timing patterns among muscles. We will dichotomize the ICP response as either “increase” vs. “unchanged/decrease”. A chi-square test will be used to assess whether the two training groups have the same proportion of participants with ICP increase, i.e., whether ACC or SS training was more effective for restoring the characteristics of post-stroke ICPs (muscle groupings and timing) to those of healthy ICPs.

Specific Aim 2b: Functional integrity of corticospinal tract during walking
Methodology and Instrumentation: We will use the frequency-based EMG analysis approach described in:
Clark DJ, Kautz SA, Bauer AR, Chen YT and Christou SA. Synchronous EMG activity in the Piper frequency band reveals the corticospinal demand of walking tasks. *Ann Biomed Eng*, 41(8): 1778-1786, 2013.
Surface EMG will be recorded from soleus (SO), medial gastrocnemius (MG), tibialis anterior (TA) and rectus femoris (RF) of both legs. EMG placement and data acquisition methodology is identical as described above for Inter-muscular Coordination.

Protocol: Participants will perform ten trials of overground walking at preferred steady state speed over a 10 meter course. Participants will then perform a number of trials in which obstacles are placed of the course and the individual will need to step over. Participants will be instructed to step over the obstacle with as little foot clearance as possible but without striking the obstacle, in order to maximize the accuracy of the task.

Analysis: Functional integrity of the corticospinal tract during walking will be quantified for each side as the difference between muscle-muscle synchrony during obstacle crossing versus during steady state walking. Data will be reduced using custom analysis programs created in Matlab (The Mathworks, Natick MA). The change in muscle-muscle synchrony between pre-training and post-training (or follow-up) will be calculated. Between-groups difference of the change value will be assessed using a regression analysis similar to Aim 1a.

6.5 Follow-Up Assessments at 3 months post-training
For each participant, we will conduct a follow-up assessment session 3 months after the conclusion of the intervention. The objective is to determine the extent to which functional gains are retained in each group, including whether the gains experienced with ACC training exceeds that of SS training. The assessments and analysis will be essentially the same as what has been proposed in Specific Aim 1.

6.6 Secondary Assessments
It is possible that assessments other than our primary assessments may help us to explain certain study findings. Furthermore, these secondary assessments include measures that are common in clinical rehabilitation and research that will help us to communicate our research findings to the field. Each assessment will be conducted at pre-intervention, post-intervention and at the 3-month follow-up session (unless noted otherwise in the description below).

Functional Independence Measure (FIM locomotor subscale): We will assess the locomotor subscale of the FIM, which uses a 7-point ordinal scale to gauge the level of assistance required to walk on a flat surface and on stairs.
Fugl-Meyer Assessment (lower extremity component): 34-point scale assessing lower extremity function through a progression of items examining more complex movements, speed, and coordination
Dynamic Gait Index: evaluates dynamic balance and the ability to adapt to changes in task demands on eight different gait tasks including: gait on even surfaces, gait when changing speeds, gait and head turns, stepping over or around obstacles, and gait with pivot turns and steps.
Environmental analysis of mobility questionnaire: The EAMQ is a self-report questionnaire, which consists of items that inquire about older adults tendencies to both encounter and avoid community mobility challenges that address several dimensions of community mobility.
Mini-Mental State Examination: a 30-point questionnaire that is used to screen for cognitive impairment.
Activities Specific Balance Confidence Scale: The ABCS is a 16-item questionnaire that gauges confidence (on a scale of 0-100%) when performing various balance and walking tasks relevant to household and community ambulation.
Charlson Index of Comorbidity: contains 19 categories of comorbidity, and will be completed from chart records. Each category has an associated weight that is based on the age-adjusted risk of one-year mortality. Higher overall comorbidity scores indicate more severe burden. This index has been used successfully to predict stroke outcomes.
CHAMPS Physical Activity Questionnaire: quantifies the approximate number of hours per week spent performing various types and levels of physical activity. It is designed to be appropriate for use with underactive individuals. We will administer the CHAMPS questionnaire at baseline and after weeks 4, 8 and 12 of the intervention. We will also administer the questionnaire at the 3-month follow-up session.
Satisfaction with mobility function and recovery: walking items from the Mobility and Self-Care (MOSES) Questionnaire will be rated on an ordinal scale to determine satisfaction pre- and post-intervention.
Working Alliance Inventory: gauges both patient's and therapist's view on the quality of the patient-therapist interaction, such as sharing common goals, maintaining trust, and sharing a common approach to problem-solving. The inventory will be conducted during the post-intervention assessment.
Quantitative assessment of walking (biomechanical, spatiotemporal and physiological parameters) will be conducted using our instrumented treadmill, motion analysis system, physiological measurement systems and GAITRite instrumented walkway. The instrumented treadmill acquires three-dimensional ground reaction forces under each foot (Bertec, Columbus OH). Kinematic data will be acquired by placing reflective markers on the participant using a modified Helen Hayes marker set and recording the movement of these markers at 100 Hz using a 12 camera motion capture system (Vicon Motion Systems). Spatial data will also be acquired using pressure-sensitive shoe insoles.
Physiological assessment will involve safe, non-invasive methods including muscle activity using electromyography (EMG), brain activity using functional near infrared spectroscopy (fNIRS) and/or electroencephalography (EEG) and stress/arousal level

using galvanic skin response (GSR). Participants may be asked to perform other tasks while walking, such as answering questions, memorizing information, carrying a tray/package, stooping to pick up an object, reaching overhead, walking over a soft mat, walking with dim lighting and/or wearing a weighted vest (not to exceed 15% of body weight or participant comfort, whichever is less).
We will ask participants to perform some tasks outside of the lab, but still on VA-approved property. These tasks may include walking on grass or other soft surface, walking up/down a wheelchair ramp, walking up/down stairs or curbs, walking in a busy corridor and walking on a concrete pathway.

6.2 Retention and Adherence to Intervention

All participants will have an initial face-to-face information session with Dr. Clark and/or Dr. Fox to foster a collaborative relationship, explain the intervention and answer questions. The importance of adherence to the intervention for optimizing therapeutic benefits will be reviewed with each participant. Monetary compensation of $20 will be paid for each therapy session attended (compensation will be tracked daily but paid on a monthly basis to minimize administrative burden). A primary purpose of this compensation is to offset expenses incurred for traveling to/from therapy sessions. If a participant misses a therapy session, a member of the study team will call him/her on the same day to schedule a make-up session. If a participant cannot complete the therapy, we will make every effort to follow him/her through the end of the trial and acquire all outcomes to the extent possible.

A study coordinator will speak with participants about unsatisfactory adherence to the therapy sessions in order to determine if there are obstacles to participation that we can assist with. Participants who consistently miss exercise sessions will be subject to withdrawal from the study at the discretion of the Principal Investigator.

6.3. Rehabilitation Interventions

Overview

The “accurate walking task” (ACC) training and “steady state walking” (SS) training interventions are designed to be similar in treatment frequency and duration, but with the distinction that ACC training will invoke a more potent, task-specific activation of the corticospinal tract due to the important role of the corticospinal tract for controlling limb placement accuracy. Both interventions will involve training on 3 days/week for 12 weeks (i.e., 36 sessions), with each session including 30 minutes of actual physical activity. Rest will be provided as needed, but will not count toward the 30 minute training time (the full session will last approximately one hour).

Training will take place in both the treadmill and overground walking environments. We will use the treadmill with safety harness because it provides a safe environment in which participants can fully test and train their capabilities without fear of fall-related injury. This is important to maximizing the intensity of training throughout the intervention period. We will use overground walking to maximize the transfer of learned skills to the “real life” walking situation (i.e., specificity of training).

All training sessions will be supervised by a licensed physical therapist who has been extensively trained in our protocols, or by a study investigator. Research assistants may also contribute to conducting training sessions under the direct supervision of the therapist or investigator. Training will emphasize independent stepping with maximal load bearing on the paretic leg and appropriate movement strategies. Occasional light hands-on cueing may be provided for tactile feedback or manual assistance to encourage appropriate movement and minimize compensatory movement. Verbal feedback will also be provided.

Randomization

We will use a stratified randomization approach, accounting for participant sex and severity of stroke. Severity will be gauged using the synergy sub-score of the Fugl-Meyer Assessment of Lower Extremity Motor Function. The synergy sub-score (0-22 points) reflects the extent to which limb control is constrained to synergistic joint movements. Stratification will ensure an even distribution of participants with higher (15-22) and lower (0-14) stroke severity in each intervention group. Randomization to an intervention group will be determined by the statistician, who will have no knowledge of the participant other than sex and Fugl-Meyer synergy score.

ACC training

This description is meant to provide an approximation of what will take place during rehabilitation. After a brief warm-up period of comfortable treadmill walking, participants will spend 15 minutes performing ACC tasks on the treadmill. They will then spend 15 minutes performing ACC tasks overground. During the first three weeks of the intervention, the ACC training tasks will be presented in a “block practice” format. That is, during a training session each task will be practiced for a few minutes before moving on to the next task. Weeks 4-6 will use a “variable practice’ format in which different ACC tasks are interspersed to make the training session less predictable and more challenging. The final six weeks of training will use a “combined practice” format in which multiple ACC tasks are performed simultaneously. For example, targeted foot placement while walking up/down from platforms and targeted foot placement during obstacle crossing.

Over the course of the intervention, training intensity will be further increased by:
1) reducing therapist assistance during ACC tasks
2) increasing number of repetitions of each ACC (less rest or “down time” between repeated trials)
3) increasing amount of limb excursion required during ACC tasks (i.e., larger obstacles, longer steps, etc.)
4) increasing speed of walking during ACC tasks

The perceived intensity reported by the participants will be quantified using the Borg CR10 Scale. Intensity and progression of training will be recorded by the therapist using a training log that will be updated throughout the training session. This log will also include overground preferred and fast walking speeds at the start of the session, treadmill speeds used during the session, description of each task, approximate number of trials performed

for each task and approximate success rate for each task. ACC tasks include, but are not limited to:

Walk over obstacles
Treadmill: A foam block will be released on the front of the treadmill belt at different phases of the gait cycle. The participant will be asked to step over the obstacle but to keep the clearance distance as small as possible in order to increase the accuracy demands of the task. Task difficulty will be modulated based on the size of the obstacle and treadmill walking speed.
Overground: Multiple foam block obstacles will be placed along walkway. The participant will be asked to step over the obstacle but to keep the clearance distance as small as possible in order to increase the accuracy demands of the task. Task difficulty will be modulated based on the size of the obstacles, number of obstacles and walking speed (preferred vs. fastest safe).
Performance goal: Walk over obstacles without striking the obstacle or losing balance, without relying excessively on therapist assistance, and without using major compensatory movements. During overground walking, speed should remain fairly stable. Use of appropriate movement patterns will be emphasized.

Walk around obstacles
Treadmill: not applicable
Overground: Obstacle will be placed along a walkway. The participant will be asked to walk around each obstacle, staying as close to the obstacle as possible without touching it. Task difficulty will be modulated based on the proximity of the obstacles and walking speed (preferred vs. fastest safe).
Performance goal: Walk around obstacles at steady speed without striking the obstacle or losing balance, without relying excessively on therapist assistance, and without using major compensatory movements. Use of appropriate movement patterns will be emphasized.

Walk up/down from platforms
Treadmill: not applicable
Overground: Task will be performed using a commercially available set of various sized platforms used in clinical practice (see photo to left). Participant will walk onto platform and then down from platform in the most smooth and continuous motion possible. Task difficulty will be modulated by changing the size and number of platforms that must be traversed.
Performance goal: Walk over platforms at a steady speed without stopping to re-adjust foot position and without major compensatory movements.

Step onto targets
Treadmill: Targeted stepping on the treadmill will be accomplished by using a laser pointer or projector (mounted on a stand) to project a target onto the treadmill belt. Participant will be instructed to place the tip of their shoe as close as possible to the target (but without “touching” it) on each step. When participants become more skilled at the task, targets will be drawn onto the treadmill belt with chalk so that the target(s) appear quickly and at an unpredictable phase of the gait cycle as the belt rotates. Task difficulty

will be modulated by changing the number of targets, location of targets (in sagittal and frontal planes) and walking speed.
Overground: Targeted stepping overground will be accomplished by placing targets made of non-slip material along a walkway. Participants will be instructed to place the tip of their shoe as close as possible to the target (but without touching it) on each step. Task difficulty will be modulated by changing the number of targets, location of targets (in sagittal and frontal planes) and walking speed.
Performance goal: Accurate targeting of foot placement without major compensatory movements while walking at a steady speed.

Foot placement ladder
Treadmill: not applicable
Overground: Task will be performed using a commercially available "foot placement ladder" that is used in clinical practice (see photo to left). The ladder has adjustable rungs that allow the therapist to modulate the difficulty of the task. Participant will walk through the ladder, stepping between rungs, in the most smooth and continuous motion possible. Task difficulty will be modulated by changing the number and orientation of rungs.
Performance goal: Traverse the ladder without tripping, without stopping to re-adjust foot position, without major speed deviations, and without major compensatory movements.

<u>SS training</u>
This description is meant to provide an approximation of what will take place during rehabilitation. After a brief warm-up period of comfortable treadmill walking, participants will spend 15 minutes walking on the treadmill at steady state speed. Speed will be set such that the intensity level yields a perceived exertion of 5 (out of a maximum of 10) on the Borg CR10 Scale, which corresponds to "hard" exertion. Participants will then spend 15 minutes walking overground at steady state pace at a similar exertion as treadmill training. Progression of training is inherently built into this protocol because, as walking ability improves, participants will be capable of walking faster at the same level of perceived exertion. Borg Scale ratings will be compared to those reported by the participants in the ACC training intervention to ensure approximate equivalence of intensity with SS training. If Borg Scale ratings are found to be non-equivalent as we conduct the interventions, we will modify the intensity of SS training to match ACC training. Intensity and progression of training will be recorded by the therapist using a training log that will be updated throughout the training session. This log will also include overground preferred and fast walking speeds at the start of the session, and treadmill speeds used during the session.

6.7. Power analysis and sample size justification
The primary objective of this study is to determine if ACC training yields a meaningful benefit over SS training for recovery of walking function in adults post-stroke. The primary outcome measure for this study is overground preferred walking speed. We seek to detect a group difference in walking speed of at least 0.11 m/s. A group difference of this size indicates a substantial clinically meaningful difference. To determine the required sample size, we used alpha = 0.05 for a one-sided test (ACC>SS), power = 0.80, and inter-individual variability of training response = 0.16 m/s (according to prior work). We also assume that at least 85% of participants will be retained to the post-intervention

assessment. Earlier studies by our group have consistently exceeded this goal. Using these parameters, we will need to enroll 64 participants (32 per treatment group). This power estimate is conservative because within-group variability is expected to be reduced after accounting for baseline characteristics (walking speed, stroke severity, co-morbid conditions, physical activity).

7. Possible Discomforts and Risks:

This study involves exercise, which can be stressful to the body. Exercise temporarily increases blood pressure and can temporarily increase the risk of heart attack or stroke. Exercise also can cause temporary shortness of breath, muscle soreness and a feeling of fatigue. There is a risk of falling, which may cause serious injuries. There is also a risk of muscle/joint injury. There is a slight risk of skin irritation due to the use of tape to secure sensors to the skin during the assessment visits. The equipment used to measure brain activity can be mildly uncomfortable when worn for prolonged periods because the sensors are spring loaded and lightly press on the scalp. To minimize discomfort we will limit the length of testing to about one hour, or will end the testing if the participant requests. Researchers will take appropriate steps to protect any information they collect. However there is a slight risk that personal information could be revealed inappropriately or accidentally. Depending on the nature of the information such a release could upset or embarrass the participant. This study may include risks that are unknown at this time

8. Possible Benefits:

Participating in this study may improve walking ability and physical fitness. However, there are no guaranteed benefits.

9. Conflict of Interest:

There is no conflict of interest.