Cortical and spinal correlates of stroke gait rehabilitation

NCT Number: NCT01668602

Protocol Date: May, 20, 2020

1. Title

Cortical and spinal correlates of stroke gait rehabilitation

2. Precis/Abstract:

Difficulty with walking is one of the most common effects of stroke. Even after rehabilitation, most stroke survivors have decreased speed, endurance, confidence, and quality of walking. Walking deficits (e.g. reduced hip, knee, and ankle flexion during swing phase, decreased forward propulsion during terminal stance) can cause risks of falls, slow walking speed, increased effort of walking, and difficulties with activities of daily living. Restoration of walking ability can improve quality of life, and is perceived as a major goal of rehabilitation by stroke survivors. There has therefore been renewed interest in research toward developing novel gait rehabilitation treatments and improving existing treatments. Examples of interventions that are used to rehabilitate walking post-stroke are functional electrical stimulation, fast treadmill walking, and bio-feedback. While recent research has focused on comparing the effectiveness of different gait rehabilitation interventions, the neural and biomechanical mechanisms underlying different gait rehabilitation strategies are unknown. Similar to pharmacological treatments, where the time course and mechanisms of the physiological responses to a specified dose of treatment are well understood, it is essential to systematically understand the mechanisms and time courses underlying gait rehabilitation*. The overall purpose of this protocol is to assess the magnitude and time course of biomechanical and neurophysiologic effects of rehabilitative strategies and protocols that are commonly used during physical therapy treatment of gait disorders post-stroke.*

As part of this protocol, study participants will participate in one of two cohorts. We will obtain systematic measurements of gait biomechanics (using 3-dimensional motion analyses), corticomotor excitability (using TMS), and walking function (using standard clinical tests of walking performance) through the course of 18 sessions of gait retraining (Cohort 1). In addition, we will investigate how different training strategies and parameters (such as electrical stimulation, fast walking speed, biofeedback) influence within-session and short-term improvements in gait biomechanics and corticomotor excitability (Cohort 2). A total of 35 individuals with stroke and 35 able-bodied individuals will be tested.

In addition to the data-collection described as part of cohort 1 and cohort 2 above, the study will also include 'pilot' or methodology-driven experiments on both able-bodied and stroke participants. These experiments do not include an intervention component and do not fall under the NIH definition of clinical trials. A majority of these pilot experiments will be conducted during the early or planning phase of the study. These pilot or methodological experiments will be utilized to test the measurement properties for the neurophysiological variables measured in the clinical trial, to evaluate short-term effects of the gait training or gait testing conditions, and to establish normative or reference values for able-bodied (as a control comparison for stroke) and stroke survivors (at baseline). The study procedures used for the pilot phase may be similar to those described for cohort 1 and 2, but only a subset of outcomes or tests may be included in the pilot phase, and a shorter duration experiment may be performed (e.g. 1 session instead of multiple evaluation or training sessions). These pilot phase data may contribute to scientific publications that inform our understanding of how methodological parameters such as posture (standing, seated), stimulation intensity, muscle state (active, rest), or timing (inter-stimulus interval between brain and nerve stimulation) influence the neurophysiologic measurements derived during non-invasive stimulation.

A subset of the able-bodied individuals may also be requested permission to utilize a brain MRI scan has already been obtained as part of a different IRB protocol. The IRB protocols that we are requesting permission to use the brain MRI scans from are two protocols whose PI (Dr Borich) is a co-investigator in the current IRB protocol: IRB00081268 (Noninvasive brain stimulation to evaluate neural plasticity after stroke) and IRB00072542 (Using concurrent brain imaging and stimulation to characterize brain behavior in stroke). The subjects will already have undergone an MRI as part of the other study protocol and if they volunteer for our study protocol, we will be able to capitalize on the MRI brain scan data obtained as part of the study to add valuable information to the current study data, This will also enable us to customize the brain stimulation to the individual's brain anatomy (for the subset of able bodied participants who have the MRI scan) and conduct a preliminary study analysis to assess correlations between brain imaging data, brain stimulation data, and walking function/biomechanics. The ability to utilize these existing MRI scans will add considerably to the depth and wealth of data collected as part of the current study without adding to subject's risks, discomfort, or time/effort. The brain scans will be used to evaluate preliminary relationships between brain structure (measured using the MRI images), walking function (measured during single or multiple sessions involving walking tasks in the gait lab), and brain excitability (measured during the brain stimulation sessions).

3. Introduction and Background:

Over 7.7 million people are living with the effects of a stroke and about 700,000 experience a stroke or a recurrence of stroke each year [1]. Stroke is the leading cause of adult disability contributing to limitations in activities of daily living [1]. More than 50% of stroke survivors have walking dysfunctions and receive gait rehabilitation[2]. Even after rehabilitation, residual gait deficits are prevalent in stroke survivors[2, 3]. Because gait dysfunction limits community mobility, most stroke survivors perceive improvement in their walking as a critical goal of rehabilitation[4, 5]. There is consensus in the literature that similar to acute stroke patients, chronic stroke patients can benefit from rehabilitation[6-13]. Thus, there has recently been renewed interest in the rehabilitation research literature toward the development and improvement of gait retraining interventions[9, 12-29].

Post-Stroke Gait Dysfunctions

Normal walking is characterized by smooth progression of steps and symmetry between limbs [30]. However, stroke results in weakness and inappropriate timing and gradation of contractions in muscles of the extremity affected by the stroke [31-34]. Post- gait deficits affect all phases of the gait cycle and all lower extremity joints[32, 34]. Common swing phase post-stroke gait deficits include reduced flexion at hip, knee, and/or ankle joints [31, 32, 34, 35]. During the stance phase, decreased contribution of the paretic leg to forward propulsion during paretic terminal stance is a critical post-stroke gait deficit shown to be correlated with hemiparetic severity, walking speed, and gait asymmetry [36, 37]. These gait deficits can lead to falls, increased energy cost of gait, and decreased endurance [5, 33, 34, 38]. Also, a slowed self-selected walking speed is one of the hallmarks of post-stroke gait, and greatly limits community participation in individuals post-stroke [39].

One goal of recent rehabilitation research has been to maximize the efficacy of post-stroke gait rehabilitation by developing new treatments and improving existing interventions[12, 16, 17, 40-42]. Recently, treadmill training has emerged as an intervention that can improve walking

performance post-stroke[2, 8, 9, 14, 15, 17, 24, 41, 43, 44]. Treadmill training enables repetitive practice of numerous steps at faster speeds on a safe terrain and improves gait patterns and symmetry [14, 45, 46]. Functional electrical stimulation (FES), the use of electrical stimulation to generate functional movements such as stepping or reaching in individuals with upper motor neuron injuries, is another excellent intervention for post-stroke gait rehabilitation[15, 20, 28, 47-52]. However, rehabilitation studies testing the effects of FES or treadmill training typically focus on demonstrating improvements in global measures of walking (e.g., speed or endurance) following 6- or 12-weeks of gait training[2, 8, 9, 14, 15, 17, 24, 41, 43, 44, 53]. While such measures are important to validate the efficacy of rehabilitation, alone, they provide no information about the motor learning processes and physiological mechanisms underlying improvements in walking function achieved with gait rehabilitation [19, 42, 54-56]. *The unique aspect of this proposed project is that, for the first time, we take the 1st step to understand the magnitude and time course of changes <u>during</u> post-stroke gait rehabilitation.*

FastFES: A Novel Gait Rehabilitation Intervention

FastFES is a novel gait training intervention that combines the beneficial effects of 2 independent interventions: Fast treadmill walking and FES. The FastFES intervention incorporates principles of physiology[57, 58], biomechanics[59, 60], motor control and learning, and predictions of forward-dynamic gait simulations[61-63] to improve post-stroke gait. *The FastFES gait treatment serves as an excellent paradigm for understanding the mechanisms underlying post-stroke gait rehabilitation because:* (1) It employs principles of motor learning (high intensity of task-specific practice, inclusion of overground walking practice, alternating walking practice with and without FES) to maximize therapeutic benefits. (2) It utilizes a scientific hypothesis-based approach to target specific post-stroke gait deficits, i.e., slowed walking speed, decreased forward propulsion, decreased knee and ankle flexion during swing. (3) It capitalizes on the use of FES as a motor learning tool to facilitate practice and learning of the proper timing and intensity of muscle activations during gait [15, 20, 21, 38, 47, 48, 64]. (4) While a typical gait rehabilitation treatment session provides practice of ~357 steps, a FastFES session may provide practice of as many as 2000 steps during one training session [65]. *Data collected on Cohort 1 of this proposed project will examine the mechanisms underlying gait rehabilitation by collecting concurrent data on gait biomechanics, corticomotor excitability, and walking function **during** a series of FastFES gait training sessions. Data collected on Cohort 2 will enable us to evaluate the within- and across-session changes induced by different types of gait training strategies including FastFES or fast walking without FES. The 2 cohorts will provide critical information that will form the foundation for future studies.*

Need for understanding the time course and mechanisms of gait rehabilitation

Although previous studies investigated the therapeutic effects gained after 6- to 12-weeks of gait rehabilitation[2, 8, 9, 14, 15, 17, 24, 41, 43, 44, 53], no information is available about when or how these performance changes evolve during rehabilitation. Are improvements in gait produced after one treatment session? What are the differences in time course of changes in biomechanical (gait kinematics and kinetics), neural (corticomotor excitability), and functional (walking speed and endurance) variables? Another interesting, important, and unaddressed question critical for designing better rehabilitation interventions is: what strategies can clinicians use to maximize improvements in gait achieved from each rehabilitation session? There is a need to systematically evaluate the differential effects of walking speeds, electrical

stimulation parameters, and biofeedback on gait training outcomes. We posit that investigating the short-term within-session changes with gait training is a more cost-effective method of gaining initial insights into response to novel treatment strategies compared to expensive large scale trials.

Animal studies show that task-specific practice of hundreds of repetitions result in reorganization of cortical motor maps and lasting changes in neural networks[66]. These neuroplastic changes in the nervous system can occur within the span of hours[67]. For instance, a study using an animal model showed that forelimb task training lead to rapid (within an hour) formation of new synapses in the motor cortex, and this synaptic neogenesis lasted long after cessation of training[67]. Similarly, if new cortical connections are activated in post-stroke adults immediately after an intensive gait rehabilitation session, we may observe resultant measurable improvements in specific gait parameters during a session and an increase in corticomotor excitability after a few gait training sessions. Also, an emerging research hypothesis is that neuroplasticity changes may be associated with greater potential for response to rehabilitation[68, 69]. Neurophysiologic measures derived using a non-invasive technique such as TMS can serve as predictors of a patient's potential for response to rehabilitation, and can guide design of more efficacious rehabilitation interventions.

In summary, there is a gap in rehabilitation literature regarding the time course of and mechanisms underlying post-stroke gait rehabilitation.

4. Objectives

The overall purpose of this protocol is to assess the biomechanical and neurophysiologic effects of rehabilitative strategies and protocols that are commonly used during physical therapy treatment of gait disorders post-stroke. As part of this protocol, 45 able-bodied individuals and 55 individuals with chronic stroke will be assigned to either Cohort 1 or Cohort 2, and will participate in 1-18 gait training sessions. If interested, study participants can also complete both study cohorts sequentially (with at least 3-weeks duration between switching from one cohort to the second). Evaluations for obtaining outcome measures will comprise clinical testing, muscle evaluations, gait analysis, and assessment of spinal and corticospinal excitability. Within Cohort 1 (stroke and able-bodied), 25 subjects will receive identical treatment throughout the training sessions (i.e. FastFES training). Within Cohort 2, 25 subjects will receive different rehabilitation strategies individually or in combination during each training session (e.g., treadmill walking, functional electrical stimulation, bio-feedback or verbal feedback about targeted walking parameters, split-belt walking, etc.). During gait training, Cohort 1 subjects will typically participate in a minimum of 2 and a maximum of 3 sessions per week. Subjects in Cohort 2 can participate in 1 to 18 gait training sessions but the frequency of the gait sessions can be varied according to the subject's and laboratory schedule (i.e. variable durations between consecutive sessions).

Aims

The aims of this protocol are to:

1) Study the changes in gait biomechanics, corticospinal excitability, and walking function during 18 sessions of gait retraining (Cohort 1).

2) Systematically determine the effect of parameters such as walking speed (slow, fast, variable, split-belt walking), functional electrical stimulation parameters (short-term changes induced by fast versus FastFES, stimulation intensity, number of muscles stimulated), and bio-

feedback on within-session changes in gait biomechanics, walking function, and corticospinal excitability (Cohort 2).

Hypotheses of the study

- By utilizing data collected on cohort 1 of subjects who undergo 18 sessions of FastFES gait retraining, the following hypothesis will be tested:

  H1. Eighteen sessions (6-8 weeks) of gait training comprising fast treadmill walking and functional electrical stimulation (FastFES) will result in Improvements in gait biomechanics, corticospinal excitability, and walking function.

  H2. Improvements in gait biomechanics will precede the improvements in corticospinal excitability and walking function.

  H3. Improvements in walking function will be correlated to improvements in corticospinal excitability.

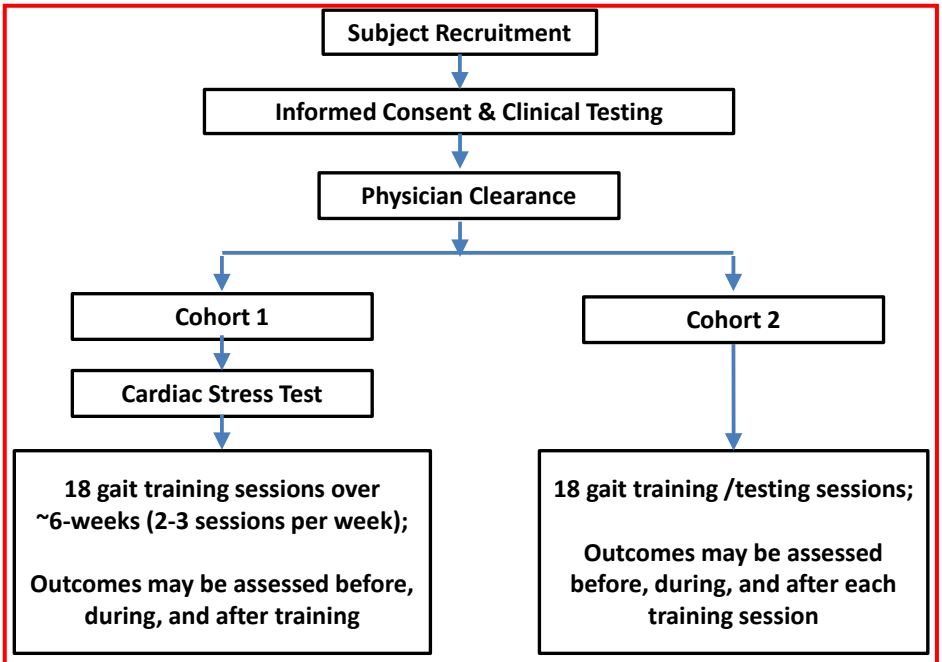
- By utilizing data collected on cohort 2 of subjects who receive different rehabilitation strategies during each training session, we will analyze short-term changes induced by 1-3 sessions of gait retraining to test the following hypothesis:

  H4. The magnitude of improvements in gait biomechanics and corticospinal excitability will be greater for gait training sessions that comprise:

  a. walking at a faster versus slower speed
  b. walking with versus without FES, i.e. Fast versus FastFES
  c. walking with FES delivered to two versus one muscle during gait
  d. walking with 2 belts going at different speeds or directions versus regular treadmill walking
  e. walking with versus without visual bio-feedback or other feedback (e.g. verbal, tactile) about targeted parameters during gait
  f. greater dosages (# of walking steps per session) of walking practice
  g. combination of 2 strategies versus a single rehabilitation strategy

5. Study design and methods

Research Procedures



Flowchart showing the overview of study procedures.

The overall goal of this protocol is to provide novel insights into the biomechanical and neural mechanisms underlying gait rehabilitation. To achieve this goal, a series of experiments will be performed on young able-bodied individuals as well as stroke survivors. The protocols to be tested and procedures to be used are described in detail here. For all the procedures and sessions described below, all testing procedures will be explained to the subject at the beginning of each testing session. Also, during these testing procedures, rest breaks will be provided to the subjects as needed and as requested by the subject. Please see the adjoining flowchart for a summary of the procedures that subjects in each study cohort will undergo. Subjects will not be randomized to the 2 cohorts. Assignment to the cohorts will be based on the lab/personnel and subject schedules. A subject can participate in the 2 cohorts sequentially. Also, participants in Cohort 2, when testing hypotheses comprising a repeated-measures comparison of different gait training strategies (e.g. Hypothesis 4a evaluating effect of walking speed; Hypothesis 4b comparing FastFES versus Fast), participants may cross-over between strategies within or across gait sessions.

1) Medical Clearance:

If a subject shows interest in participation in cohort 2 of the study (18 training sessions), before participation, we will obtain written medical clearance from the subject's physician (See attached Medical Clearance form). In addition, the subject will undergo clinical assessment to confirm that they are eligible for study participation.

2) Procedures for Clinical Assessment of Walking Function and Muscle Strength:

All subjects will review and sign consent forms before clinical testing. Clinical Testing will be performed by a licensed physical therapist. Clinical testing may comprise: (1) measurement of subjects' over ground self-selected (SS) walking speed (6-meter walk test); (2) over ground walking endurance measured by the distance ambulated during the 6-minute walk test; (3) assessment of gait and dynamic balance (measured using the functional gait assessment, 4-square step test, and the Berg balance score); (4) lower extremity portion of the Fugl-Meyer score[70]; (5) step activity monitoring; (6) lower extremity proprioception (in which each limb segment will be flexed or extended approximately 10 degrees and the subject will be asked to identify whether the limb is moving and in what

direction); (7) Lower extremity sensation utilizing monofilaments. Each limb segment will be tested and the smallest diameter filament that can be felt reliably (4 out 5 trials) will be recorded. Additional clinical measures may include measures of cognitive impairments and self-reports (e.g. Stroke Impact Scale, Walk-12 questionnaire, Activity-specific Balance Confidence Scale, reports of physical activity levels). These measurements will provide an assessment of the severity of subject impairments. In addition, the subject's fast walking speed will be determined as the fastest speed the subject can attain during a 4-minute bout of treadmill walking. For able-bodied subjects, the clinical testing may not be performed or may only comprise a subset of the outcomes listed above.

In addition, during this session, after completion of clinical testing, ***assessment of muscle strength*** may be performed using procedures described below.

Muscle strength of the subjects' bilateral knee extensor, knee flexor, ankle plantarflexor, and ankle dorsiflexor muscle groups will be evaluated.

Positioning for Measurement of Knee Strength: For evaluating the knee muscles, the subject will be seated on a force dynamometer with the hips and knees bent at approximately 90 degrees. The subject's leg will be strapped to the arm of the dynamometer. In addition, inelastic belts will be used to strap the subject's trunk and thigh to the dynamometer chair for stabilization. The subject will be asked to 'kick out' (for knee extensors) or 'pull in' (for the knee flexors) with the leg being tested with as much force as possible.

Positioning for Measurement of Ankle Strength: For evaluating the ankle muscles, the subject will be positioned supine on the force dynamometer with the hips and knees extended, and the foot strapped to the dynamometer arm. The shank, thigh, and trunk will be stabilized using inelastic straps. The subject will be asked to 'pull the foot in' (for the ankle dorsiflexors) or 'push the foot down' (for the ankle plantarflexors) with as much force as possible.

Burst superimposition during muscle strength testing: A technique called the burst superimposition technique will be used for measurement of the subject's muscle strength. This technique has been used to safely obtain a quick and accurate measurement of muscle strength in young and elderly able-bodied individuals as well as patient populations[71-73]. For this technique, while the subjects are generating their maximal contraction force volitionally, a supra-maximal burst of electrical stimulation (100-Hz frequency, 100-ms duration, 600 μs pulse duration) will be delivered to the muscle. The force generated by the muscles will be recorded via a force dynamometer. The 'true' force generating ability of the muscle will be calculated as the total force generated by the subject's volitional contraction and the superimposed electrical stimulation. The maximal contraction will be repeated 2 times for each leg.

3) Cardiac Exercise Stress Test:

After confirming the subject's eligibility for participation in the study and clinical testing, if the subject is part of Cohort 1 that will participate in the intensive 18-sessions of gait training, the subject will be referred for a cardiac exercise stress test (treadmill exercise test). The exercise stress test will be conducted under the supervision of a cardiologist at Emory University (referral will be provided as part of this research protocol). The stress test will help confirm that the subjects who participate in the intensive gait training

treatment sessions have sufficient cardiovascular health to participate in a treadmill exercise intervention. If a participant is unable to complete the stress test due to musculoskeletal impairments or other factors unrelated to cardiac health (e.g. muscle weakness, ankle instability, inability to walk at sufficiently fast speed or incline due to post-stroke muscle weakness), then the tolerance and appropriate dosage for treadmill training will be determined based on consultation with the cardiologist, exercise physiologist, and physical therapists.

4) Procedures for Gait Training Sessions:

For gait training, as part of Cohort 1, the subject will receive the same type of walking training (fast treadmill walking with electrical stimulation) for all 18 sessions and participate in 2-3 training sessions per week over the course of 6-weeks. For cohort 1, the gait training sessions may comprise up to six 6-minute bouts of walking with rest breaks between bouts (total 30-minutes of walking). The last training bout (bout 6) may comprise 6-minutes of over ground walking (Fig. 1), during which subjects will be asked to walk as fast as they can. For safety, a physical therapist will walk with and guard the subject during over ground walking. For cohort 1, outcome measures may be obtained before, after, and intermittently throughout the 6-weeks of training (e.g. clinical testing, muscle strength testing, and assessment of corticospinal and spinal excitability).

Subjects in Cohort 2 will receive different types of walking training (e.g. treadmill walking at slow or fast speed, training with (FastFES) or without stimulation (Fast), training with or without feedback, etc.) for each of the training sessions, and will complete 1-3 training session per week with a variable delay (1-day to several weeks) between consecutive sessions. For cohort 2, outcome measures may be obtained before, after, and intermittently during each of the training sessions (e.g. clinical testing, muscle strength testing, and assessment of corticospinal and spinal excitability). For Cohort 2, when the subject receives different types of training during each of the 18 sessions, the training may comprise a total of 10 to 40-minutes of different types of walking. Depending on the gait training strategy being tested during the session, the session may comprise one or more of the following:

- Treadmill walking at a range of walking speeds (ranging from slower than comfortable self-selected speed to the subject's fast walking speed)
- Electrical stimulation applied to the ankle muscles at appropriate phases of the gait cycle during gait training
- Walking with both treadmill belts running at different speeds or directions
- Greater versus smaller dose of walking practice (three versus six 6-minute bouts)
- Bio-feedback, visual cues, or verbal / tactile cues regarding specific parameters of gait such as push-off forces, knee flexion angle during swing phase, etc.

Note that data from Cohort 1 (case series on FastFES gait training) as well as data that evaluate Hypothesis 4b (i.e. a repeated-measures comparison of the short-term effects of FastFES versus Fast on corticospinal excitability and gait biomechanics) will inform the methodology, planning, and sample-size estimation for a future larger clinical trial.

At the beginning and end of each training session, a "**pre-test**" and "**post-test**" may be performed. The pre- and post-tests will comprise 30-second trials of treadmill walking at the subject's comfortable or fast walking speed. By obtaining data while

training at a standardized walking speed and while training without FES, we will be able to measure differences in motor learning among these training strategies. The procedures for motion analyses to be used for pre- and post-tests are described in a separate section (Procedures for Motion Analyses). In addition, for a few sessions, in addition to the 30-second walking trials, the pre- and post-test may comprise assessment of spinal or corticospinal excitability.

During the training sessions, subjects may wear a harness suspended from the ceiling (no body-weight support) for safety. In addition, if needed, the subjects will be allowed to hold on to the hand rails during walking. For stroke survivors, heart rate will be monitored throughout the session with a heart rate sensor that is placed on the chest under clothing (Polar USA, Lake Success, NY). If heart rate exceeds 80% of their age predicted heart rate maximum, walking will be stopped until it returns to baseline. In addition, blood pressure will be monitored at each rest break. If a subject's blood pressure exceeds 190/100 mmHg, the session will be stopped and their blood pressure will be continually monitored until it returns to baseline. Subjects will rate their perceived exertion on the Borg Scale of Perceived Exertion every 6 minutes. If a subject reaches level 13 on the Borg scale (i.e. between 'Fairly Light' and 'Somewhat hard') they will be given a rest break[74].

5) Procedures for Motion Analysis:

During this session, retro-reflective markers will be attached to the subjects' lower extremities[59, 60]. Elastic bands (Fabrifoam, USA) will be wrapped around the thighs, calves and pelvis to which small, thermoplastic shells containing reflective markers will be attached. Additional markers will be taped to the subjects' shoes and on the upper back, shoulder, hip, knee, and ankle joints with adhesive skin tape. Marker data will be collected using a 7-camera motion analyses system at 120-Hz (Vicon, Oxford, UK). During treadmill walking, ground reaction forces during treadmill walking will be collected using a treadmill instrumented with two 6-component force platforms under each belt (Bertec, USA). During over ground walking, ground reaction forces will be collected using a force plate embedded within the lab floor (AMTI, USA). In addition, in order to record muscle activity, small electromyography (EMG) sensors may be attached to various muscles. The EMG sensors will be attached using hypo-allergenic adhesive. EMG signals will be recorded from the following muscles: tibialis anterior, soleus, gastrocnemius, quadriceps femoris, hamstrings, gluteus medius, and erector spinae. Foot switches (25-mm diameter MA-153, Motion Lab Systems, LA) will be attached bilaterally to the soles of the subjects' shoes - one on the forefoot approximately under the fifth metatarsal head and another on the hind foot under the lateral portion of the heel[59, 60]. All analog data (force platform, EMG, footswitch, and stimulation channels) will be collected at 2400-Hz.

Motion analysis data will be collected during 1- to 10-second long static postures (standing and sitting). In addition, 15- to 40-second long dynamic trials will be recorded as subjects walk over ground or on a treadmill. During treadmill walking, subjects will wear a ceiling-mounted safety harness during all trials. An emergency shut-off switch will be positioned within arm's reach of the experimenter and can be used at any time by the experimenter to stop the treadmill. Subjects will be allowed rest breaks as often

as requested. Similar to the procedures described for the training sessions, subjects' heart rate, perceived exertion, and blood pressure will be monitored during the session.

6) Procedures for Functional Electrical Stimulation:

Surface electrical stimulation electrodes will be attached to the ankle dorsiflexor (2"X2", TENS, CO) and plantarflexor muscles (3"X5", VersaStim, ConMed Corp, NY). For the dorsiflexors, the cathode will be placed over the motor point of the tibialis anterior and the anode over the distal portion of the muscle belly of the tibialis anterior. For the plantarflexors, the cathode will be placed over the proximal portion and the anode over the distal portion of the gastrocnemius muscle belly. Next, stimulation intensity to be used during walking will be determined for each muscle. For ankle dorsiflexor muscles, intensity will be set to generate ankle dorsiflexion to a neutral ankle position when the subjects are seated with their leg suspended. For the ankle plantarflexor muscles, the intensity will be set to achieve lifting of the paretic heel off the ground, with the subject in a standing position[60]. Maximal intensity will also be set based on subject tolerance.

An electrical stimulator will be used to deliver stimulation during walking (Grass S8800 stimulator with SIU8TB stimulus isolation unit; UDel stimulator). A customized, real-time system [59, 60, 75] (CompactRIO, National Instruments, TX) will be used to control the stimulator and deliver stimulation during appropriate phases of the gait cycle. Stimulation will be delivered to the ankle dorsiflexors when the subject's foot is in the air (swing phase). Stimulation will be delivered to the ankle plantarflexors during the terminal stance phase of gait. 30-Hz variable frequency stimulation trains [58] will be delivered during gait.

7) Procedures for Assessment of Spinal Excitability:

Spinal excitability may be assessed using peripheral electrical stimulation delivered to the nerves innervating the ankle muscles. The methods for electrical stimulation are similar to those used for delivering functional electrical stimulation except that the subjects are seated and the stimulation is used to obtain outcome measures assessing spinal excitability. The spinal excitability measures do not introduce any new or additional risks or benefits to the study participants beyond those caused by the current study procedures. Muscles of interest are the soleus and medial gastrocnemius (calf muscles), and tibialis anterior (front of lower leg). After cleaning the skin with alcohol and preparing the skin over the muscles, self-adhesive electromyography (EMG) electrodes will be applied to the skin overlying the muscles. An electrical stimulation electrode (2 inches by 2 inches) will be placed in space just above the knee, and used as the anode for tibial nerve stimulation. The subject's EMG activity will be recorded while a cathode is moved at the back of the knee to determine the location that provides the best EMG response. A self-adhesive stimulating electrode will be placed at the cathode location that yields the best EMG response. Electrical stimulation electrodes will be placed on the front of the leg, immediately lateral and under the knee (for deep peroneal nerve stimulation); and on the posterior aspect of the medial gastrocnemius muscle, 7-10 cm below the popliteal fossa (for medial gastrocnemius nerve stimulation). EMG activity will be recorded while 50-60 electrical stimuli (short 1 ms square pulses, ranging in intensity from 1mA – 80 mA), 7-10 seconds apart, are delivered to the muscle. We may also deliver 5-20 electrical stimulus

pulses at intensities that elicit a percentage of the maximum reflex response. In addition, the electrical stimulus pulses may be delivered paired with a pulse delivered to the same or antagonist muscle, or as the subject maintains a low-level contraction with the target or antagonist muscle. The spinal excitability measures may be obtained during the same session as the corticospinal measures and may be paired at variable delays with the TMS pulses during assessment.

8) Procedures for Assessment of Corticospinal Excitability:

Corticospinal excitability will be assessed using a non-invasive technique called transcranial magnetic stimulation (TMS). TMS will be delivered using MagStim Stimulators with a double circular coil, custom-built double-cone or batwing coil (Magstim Ltd, Wales, UK). Electrical activity from muscles in response to the TMS will be collected using surface EMG electrodes attached to muscles that play critical roles during walking (e.g. quadriceps femoris, tibialis anterior, soleus, gastrocnemius, hamstrings, etc). In addition, EMG signals will be recorded from a couple of upper extremity muscles (e.g. first dorsal interosseus, flexor digitorum indicis) to be used as a control. First, the site on the scalp where a TMS pulse of ~30 to 60% maximum stimulator output produces the greatest muscle response (hotspot) will be identified for a target muscle [76]. The motor threshold intensity will be identified for the target muscle. After this, TMS intensity may be set at 120% motor threshold and motor mapping data collected as single pulses of TMS are delivered to different areas of the scalp. Subjects will wear a closely fitting cap containing 1-cm grids in antero-posterior and medio-lateral orientations. During mapping, 10 consecutive stimuli will be delivered at scalp locations at 2-cm distance intervals. Next, single TMS pulses of a range of intensities (0 to 100% maximum stimulator output) will be delivered in a random order (one pulse every 3-5 seconds) at the hotspot location for the targeted muscle. These data will be used to plot the TMS recruitment curve, i.e. the relation between stimulation intensity and the EMG amplitude. Next, the muscle's maximal contraction muscle activity level will be determined by asking the subjects to contract their muscle as hard as possible. Additionally, a paired-pulse data may be collected to determine the magnitude of intracortical inhibition and facilitation of the primary motor cortex bilaterally. TMS will be delivered using two Magstim 200^2 stimulators connected via a BiStim^2 module (Magstim Co., Wales, UK). Conditioning pulses will be delivered a range of intensities (75-155% of the active motor threshold determined for the target muscle). The intensity of the test stimulus will be set to the percentage of TMS stimulator output that elicits an MEP of 1 mV. Inhibition will be indexed with interstimulus intervals of 2 ms; facilitation at 12 ms. Twenty stimuli will be delivered for each conditioning stimulation intensity (10 conditioned at 2 ms, 10 conditioned at 12 ms). Twenty non-conditioned, single-pulse stimuli will also be delivered during the paired-pulse TMS assessment. Comparing mean peak-to-peak MEP amplitudes of the conditioned and non-conditioned stimuli will be used to index short intracortical inhibition and facilitation. Additional TMS data may be collected as the subjects maintain a low level contraction from the muscles (~10% maximal EMG level). This part of the study is optional and as part of the consent process, the subjects will be able to choose to participate in the remaining study procedures and opt out of the brain stimulation portion of the study.

Procedures for MRI Scans (for a subset of 15 able-bodied individuals):

As stated above, the MRI scans will be obtained as part of a different IRB protocol. The IRB

protocols that we are requesting permission to use the brain MRI scans from are two protocols whose PI (Dr Borich) is a co-investigator in the current IRB protocol: IRB00081268 (Noninvasive brain stimulation to evaluate neural plasticity after stroke) and IRB00072542 (Using concurrent brain imaging and stimulation to characterize brain behavior in stroke). The methods for the MRI will be as described in the above protocols, and for convenience are also listed here.

MRI acquisition: Scanning will be conducted at Emory University at the Center for Systems Imaging on a Siemens 3T Trio whole-body MRI scanner. A high-resolution T_1 scan (TR = 7.4ms, TE = 3.7ms, flip angle $\theta = 6°$, FOV = 256mm, 160 slices, 1 mm thickness, scan time=3.2min) will be performed without contrast. The study team will have direct and immediate access to the data using Emory University's secure network server.

Risks

Risks associated with clinical testing, gait training, and motion analyses include falling, fatigue, poor heart rate and blood pressure response to walking and minor skin irritation from the adhesive tape. To minimize risk, subjects will wear a safety harness during the treadmill testing and will be given a rest break whenever requested. Heart rate will be monitored continuously and blood pressure will be monitored at rest breaks. If heart rate exceeds 80% of their age predicted heart rate maximum, walking will be stopped until it returns to baseline. If a subject's blood pressure exceeds 190/100 mmHg, the session will be stopped and their blood pressure will be continually monitored until it returns to baseline. The subject's primary or referring physician will be notified. Throughout the experiment, the experimenter has access to an emergency safety switch that can be used to stop the treadmill immediately. To ensure sufficient cardiovascular health to complete an intensive gait training program, stroke subjects who participate in 18 sessions of gait training (Cohort 1) will complete a cardiac exercise stress test.

Risks associated with electrical stimulation: After electrical stimulation to the ankle or knee muscles, subjects may experience some muscle soreness for about 2 days that is similar to the muscle soreness if someone lifts weights or exercises vigorously after a long break. During electrical stimulation, the potential for equipment malfunction is also present, which might result in burns to the skin. However, the equipment used is highly reliable and prolonged exposure necessary to cause the risk of skin damage is highly unlikely with the stimulation parameters used in this experimental design. Risks associated with measurement of spinal excitability using peripheral stimulation are similar to the risks associated with electrical stimulation listed here.

Risks associated with the use of TMS to assess corticospinal excitability: Seizures are a rare reported risk with TMS. The current study involves single-pulse TMS at low frequency (< 0.2 Hz), which has been used for over 20 years in a variety of normal subjects and in subjects with neurological conditions and has been found to be safe. Safety precautions and practice recommendations for TMS research are summarized in publications; and these guidelines will be followed in our current single-pulse TMS protocol.[77-80] Based on a recent Consensus paper (meta-analysis / review of TMS literature), to date, more than 5000 research papers have been

published using single-pulse TMS; only 2 cases of seizures have been reported with single-pulse TMS [81-83]. In addition, Gilbert et al showed that in 38 studies involving 850 subjects including children with cerebral palsy and other neurological conditions, there were no seizures or other major adverse events [77]. Another recent review concluded that the safety of single-pulse TMS in clinical practice, including as an acute migraine headache treatment, is supported by biological, empirical, and clinical trial evidence [80]. TMS rates used in our study, of 0.2 Hz or less, are safe in epileptic patients [84]. However, to take additional steps to minimize risks, we will not include any individuals with a history of seizures in our study. In addition, during TMS, subjects may feel twitches in the muscles of arm, leg or face during the magnetic stimulation, but these twitches should not be painful. There is a rare possibility of headaches, scalp discomfort, dizziness, or light-headedness. If they occur, these effects are usually mild and short-lasting. Recently, a research of literature showed recent publications providing case reports of episodes of syncope or seizure during single-pulse TMS in able-bodied individuals[85-87]. To prevent the risk of syncope, vaso-vagal stimulation, or dizziness in the current study, we will exclude subjects if they have a history of syncope, dizziness, loss of consciousness, or nausea in the past 12 months, including but not limited to syncope triggered by drawing blood. Metal and conductive objects close to the coil may move during magnetic stimulation. A click during magnetic stimulation may be heard. The subjects may be provided with foam earplugs that can prevent any discomfort from this clicking noise. There is also a risk of mild skin redness or irritation at the location where the muscle sensors have been placed, but this will usually go away quickly after sensors are removed.

Risks associated with assessment of muscle strength include fatigue, muscle soreness, strains in the muscles surrounding the hip, knee, ankle or foot.

Potential Benefits

Although these procedures are experimental, and the responses of individual subjects to the gait training sessions may vary widely, the subjects may experience small and short-lasting increases in their walking speed, endurance, or balance as a result of these treatments. Also, the long-term findings of this study can help us better understand the effects of and guide the design of clinical rehabilitation which can benefit other stroke survivors in the future.

Type of Information Collected

During clinical testing, to help characterize the clinical characteristics of the subject group, information such as age, time since the stroke, height, weight, side of hemiparesis, etc. will be collected. To help characterize the level of impairment of the subject group, information such as walking speed, endurance, walking function score, lower extremity sensation, etc. will be collected. During motion analysis and gait training, the 3-dimensional camera system will be used to track the 3-D positions of the subject's segments; these data will be used to compute joint angles, ground reaction forces, joint moments, joint powers, etc. During strength testing, the force generated by the subject's joints will be measured. During assessment of corticospinal excitability via TMS, the EMG sensors attached to the muscles will record the level of muscle activity in response to the TMS pulses. All subject data will be de-identified and then compiled on an excel spreadsheet and imported into SPSS 14 (SPSS, Chicago, IL) for statistical analysis. De-identified data will be disseminated through group discussions, presentations and publications.

Management of Subject Data
Subjects will not be anonymous to the researchers. As a first step during data management, subject identities will be de-identified by assigning each subject a number. Any computer files containing information that link the identifiable subject data with the de-identified subject number will be password protected and stored on a secure Emory University computer. Only de-identified data will be used to compile spreadsheets of the various outcome measures collected as part of this study (joint angles, clinical impairment scores, EMG, etc.). De-identified data may be stored for future use until 5-years after completion of the study. All signed consent forms will be stored in the subject's folder (organized by de-identified subject numbers) in a locked file cabinet at the University. Participants will not be audiotaped, photographed or videotaped without their permission during this study.

6. Participant selection
We plan to collect data on a sample of 55 individuals post-stroke and 35 able-bodied individuals. However, we anticipate a withdrawal rate of ~10%. Therefore, we will recruit 60 subjects and 45 able-bodied subjects.

Inclusion Criteria for Post-Stroke Subjects are: 1) age 30-80 years, 2) chronic stroke (>6 months post stroke), 3) first (single) lesion, 4) ambulatory with or without the use of a cane or walker, 5) sufficient cardiovascular health and ankle stability to walk for 6 minutes at their self-selected speed without an orthoses, 6) resting heart rate 40-100 beats per minute, 7) resting blood pressure between 90/60-70/90.

Exclusion Criteria for Post-Stroke Subjects are: 1) evidence of moderate/ severe chronic white matter disease or cerebellar stroke on MRI, 2) cerebellar signs (ataxic ("drunken") gait or decreased coordination during rapid alternating hand or foot movements, 3) insulin dependent diabetes, 4) history of lower extremity joint replacement, 5) score of >1 on question 1b and >0 on question 1c on NIH Stroke Scale, 6) inability to communicate with investigators, 7) neglect/hemianopia, or unexplained dizziness in last 6 months, 8) neurologic conditions other than stroke, 9) orthopedic problems in the lower limbs or spine (or other medical conditions) that limit walking. Additional exclusion criteria for TMS (measurement of corticospinal excitability) are: 10) history of seizures, 11) metal implants in the head or face, 12) history of recurring or severe headaches/migraine, 13) headache within the past 24 hours, 14) presence of skull abnormalities or fractures, 15) hemorrhagic stroke, 16) history of dizziness, syncope, nausea, or loss of consciousness in the past 12 months.

Inclusion Criteria for Able-Bodied Individuals are: 1) age 21 to 80 years, 2) no history of neurologic disease, 3) no history of orthopedic disease or injury affecting the lower extremity.

Exclusion Criteria for Able-Bodied Individuals are: 1) history of neurologic disease, 2) history of orthopedic disease or injury to the lower extremity, 3) an implanted cardiac pacemaker. Additional exclusion criteria for the TMS portion of the study (corticospinal excitability measurement) are: 4) history of seizures, 5) metal implants in the head or face, 6) history of recurring or severe headaches/migraine, 7) headache within the past 24 hours, 8) presence of skull abnormalities or fractures.

Subject Recruitment. Study participants will be recruited from the general community within and outside Emory University.

Withdrawal from study. Participation in the present study will be voluntary and subjects will be able to opt out of the study at any time.

Our subject population will be representative of adult patients with stroke and healthy adults. The incidence of stroke is considered rare in children, estimated to be less than 13 cases per 100,000 children[88] and their inclusion would not provide additional information compared with the data gathered in adults.

7. Statistical analysis

Hypotheses testing will be done with a p-value set at 0.05. The outcome variables used for analyses will include peak knee and ankle flexion during walking, propulsive forces during walking, walking speed and endurance, peak and duration of EMG activation during walking, and TMS-derived measures of corticospinal excitability (peak EMG in response to TMS, motor threshold intensity, slope and peak of the TMS-recruitment curve). To test *H1*, for each of the variables, one-way repeated measures ANOVA will be performed to check for differences in the variable after versus before 18 sessions of training. To test *H2*, we will plot the dependent variable versus time (test session number). Using these plots, the time to plateau and the time when the variable first shows a positive within-session change (threshold time) will be determined. One way repeated measures ANOVA will be used to compare the time to plateau and threshold time among 3 variables – peak propulsion, peak TMS muscle response, and over ground walking speed. To test H3, a pearson's correlation will be performed between the change in peak propulsion after training versus change in peak TMS muscle response after training. For the hypothesis involving within-session changes (*H4*), repeated measures ANOVA will be performed to compare the within-session percentage change for each variable between different rehabilitation strategies.

Power Analysis: The current protocol has been powered using the primary outcome measure of paretic propulsive force generation. Based on means and standard deviations from our existing pilot data, for each aim, a sample of 24 subjects will provide 80% power to detect a 4.2% difference in propulsive force between sessions with standard deviation of 6% at a two-sided alpha level of 0.05. After completion, the data from this study will be used to conduct systematic power analysis for other outcome variables, which will be utilized to design a larger-scale future study.

8. Adverse event reporting

We will notify the IRB of any adverse events that occur during the protocol.

10. Device information

Equipment for Motion Analysis and Gait Retraining: A 7-camera system will be used to collect motion analysis data (Vicon, Oxford, UK). Ground reaction forces during treadmill walking will be collected using a treadmill instrumented with two 6-component force platforms under each

belt (Bertec, USA). During over ground walking, ground reaction forces will be collected using a force plate embedded within the lab floor (AMTI, USA). In addition, small electromyography (EMG) sensors will be attached to various muscles to collect EMG data (Noraxon Inc., Arizona, USA). The EMG sensors will be attached using hypo-allergenic adhesive. Pressure-sensitive foot switches (25-mm diameter MA-153, Motion Lab Systems, LA) will be attached to the underside of the subjects' shoes; the foot switch data will be used to record gait events (Noraxon Inc, Arizona, USA). All these devices widely used for measurement of human movements.

Electrical Stimulation Equipment: Electrical stimulation will be delivered non-invasively via electrodes attached on the skin overlying the targeted muscle (ankle dorsi- and plantar-flexor muscles). Square electrical pulses of pulse durations upto 800-μs, pulse amplitudes upto 150 Volts, and frequencies ranging from 1 to 100-Hz will be delivered. Electrical stimulation will be delivered using a Grass S8800 or S4800 stimulator (Grass Technologies Inc., RI, USA). To ensure subject safety, the stimulator will be used in conjunction with a transformer isolated, constant voltage SIU8T stimulus isolation unit which is designed to be used for research nerve and muscle constant voltage stimulation (Grass technologies Inc., RI, USA).

Transcranial Magnetic Stimulation Equipment: Magnetic stimulation will be delivered using a MagStim 200 unit (MagStim, Dyfed, UK). A custom bat-wing or double cone coil will be positioned over the scalp at the optimal site for activation of the target muscle. TMS is a safe and painless technique for investigating the excitability of neuronal tissue within the brain. In brief, a magnetic stimulus delivered via a coil held over the scalp is utilized to excite the neural tissue of the brain located beneath the coil. The coil is positioned appropriately to stimulate the area of the motor cortex that controls specific target muscles. Magnetic stimulators are commercially available, and the safety of their use with neurologically intact and neurologically impaired populations has been well documented. TMS has been utilized in several previous studies by the investigators including use with neurologic populations.

11. References and appendices

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