Study Title: Using tDCS to Jump Start Gait Training in Chronic Stroke Patients

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Study locations 1. University of Arkansas for Medical Sciences
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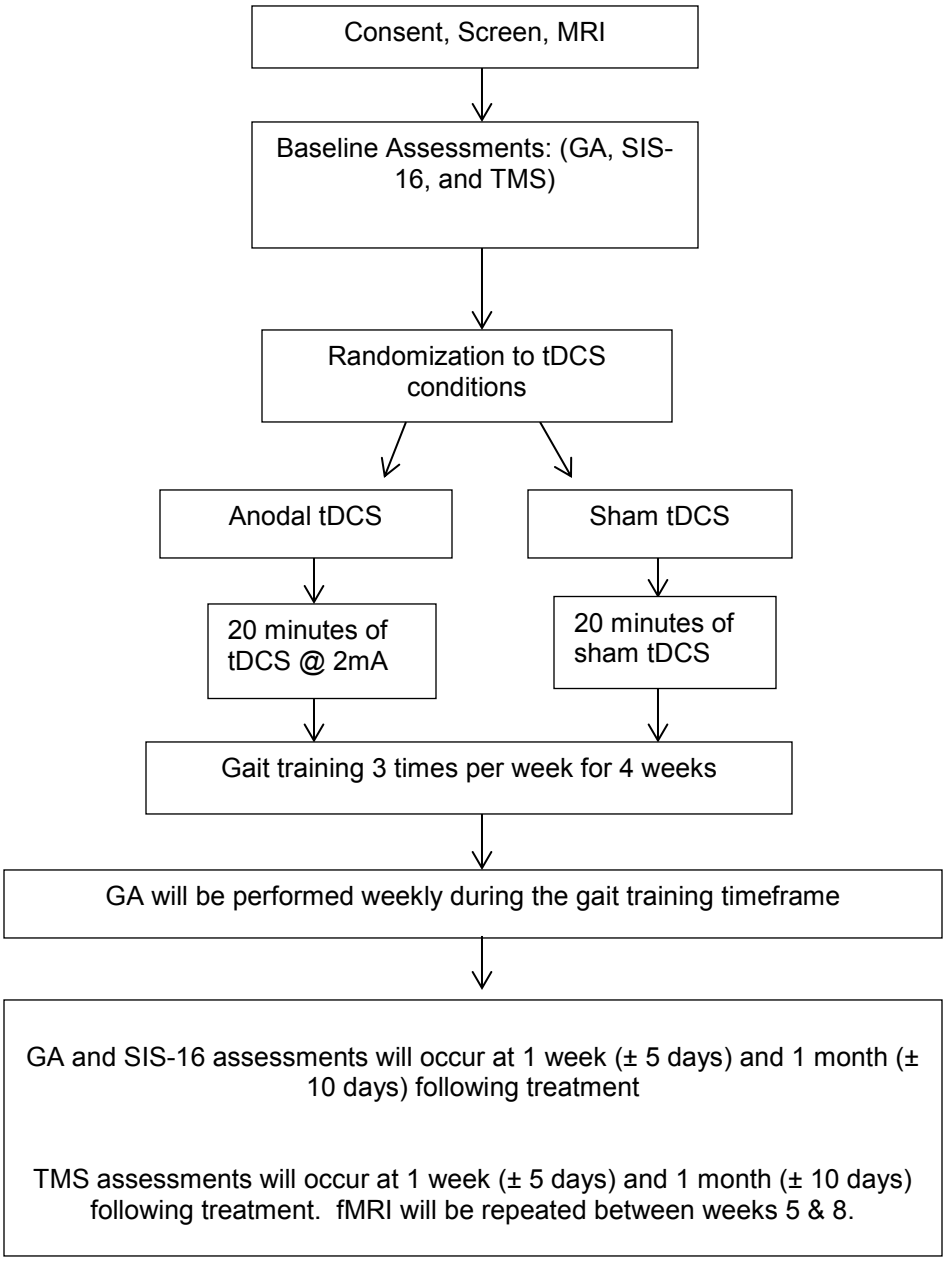
Core Research Facility, Center for Translation Neuroscience,UAMS

2. University of Central Arkansas
Movement Analysis Laboratory, Department of Physical Therapy, UCA

Study Schema



Abbreviations: tDCS= transcranial direct current stimulation, GA= gait assessments (performed at UCA), SIS= Stroke Impact Scale (performed at UCA), TMS=transcranial magnetic stimulation (performed at UAMS). MEP= motor evoked potential

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Abbreviations

ANOVA=Analysis of Variance
Botox=botulinum toxin
CNS=central nervous system
The control group (C)=the group receiving sham tDCS.
tDCS = transcranial direct current stimulation
anodal tDCS = positive charge associated with cortical activation
cathodal tDCS = negative charge associated with cortical inhibition
EMG = electromyography
FAC=Functional ambulation category
ECT= electroconvulsive therapy
EEG=Electroencephalography
EMG=Electromyography
Hz=Hertz
The intervention group (I) = the group receiving active tDCS
IRB=UAMS Institutional Review Board
LED=Light-emitting diode
mA = milliamp
MEP = motor evoked potential
MEPmax=Motor evoked potential maximum
MRI=Magnetic Resonance Imaging
MT=motor threshold
MVC=maximum volitional contraction
NICE=UAMS New Investigation Consult and Education
NINDS=national institute of neurological disorders and stroke
NIH=National Institutes of Health
NMES=neuromuscular electrical stimulation
SIS=Stroke Impact Scale
TA=tibialis anterior muscle
TASS=Transcranial Magnetic Stimulation Adult Safety Screen
TMS = transcranial magnetic stimulation
rTMS = repetitive tanscranial magnetic stimulation
ORC=UAMS Office of Regulatory Compliance
UAMS=University of Arkansas for Medical Sciences
UCA=University of Central Arkansas

Protocol Summary

Rationale: Approximately one third of stroke patients with hemiparesis are unable to walk without assistance. Mobility limitations exert a huge physical, financial, and emotional burden on stroke survivors. Costs associated with decreased mobility are estimated to be in the tens of billions of dollars. Conversely, regaining mobility greatly improves the quality of life of stroke survivors. Consistent with directives of the National Institute of Neurological disorders and Stroke (NINDS), this project uses neuromodulation as a treatment to enhance gait recovery in chronic stroke patients. Specifically, we will examine whether transcranial direct current stimulation (tDCS) can augment the beneficial effects of a gait training program.

As stroke can reduce a patient's capacity for increased cortical excitation, we aim to use anodal tDCS to increase cortical excitability during gait training. tDCS is a noninvasive neruomodulatory device that passes a low voltage current across the scalp and underlying brain tissue and can either increase or decrease cortical excitability depending on how it is applied.

Study: We will block randomize 88 chronic stroke patients to two treatment arms. Persons will be block randomized into anodal and sham tDCS conditions. Persons in the anodal tDCS condition will receive 20 minutes of stimulation and persons in the sham condition will receive 20 minutes of sham stimulation. All patients will receive gait training using a body weight supporting treadmill. In over ground assessments at baseline, weekly during gait training sessions, and one week, and one month post treatment, we will measure 1) gait velocity and spatiotemporal gait parameters using the GAITRite electronic walkway and 2) ankle,knee, and hip angles using motion analysis to gauge changes in the gait pattern. Cortical excitability will be measured at baseline, one week, and one month post treatment using transcranial magnetic stimulation (TMS). Functional MRI will be measured at baseline and after treatment between weeks 5-8. Additionally, we will measure change in physical function and social well-being using the Stroke Impact Scale and we will define patient characteristics that are associated with response to treatment.

Significance: If successful, this study will augment gait recovery and potentially increase the number of patients who benefit from gait training. Our methodological innovations will have application to a wide variety of neurological conditions.

Background and Rationale

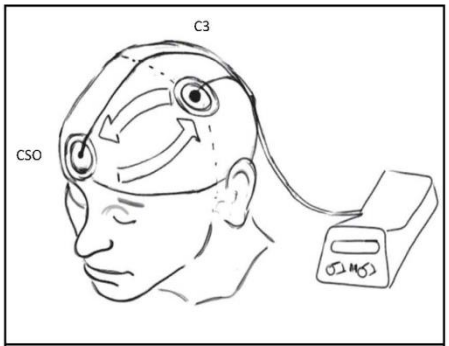
Stroke is the leading cause of disability in the United States affecting 13 million people [1, 2]. Up to two thirds of stroke survivors have significant limitations impairing their ability to walk[3] including slow gait speed[4] and changes in the quality of the gait pattern[5]. Additionally, individuals with a stroke and limited mobility are at high risk for susbsequent complications including falls[6], fractures[7], and a further decline in mobility[8]. In contrast, recovering the ability to walk greatly improves quality of life and can return individuals to a previous level of productivity [9-12]. Our proposal aims to use tDCS to

"jump start" the beneficial effect of gait training. This proposal is responsive to research priorities of the NINDS.

An NINDS Stroke Progress Review Group (PRG) first convened in 2001 to prioritize its' unmet scientific needs and research opportunities. The group reconvened in 2011 to issue an updated report (http://www.ninds.nih.gov/find_people/groups/stroke_prg/2012-stroke-prg-full-report.htm#RR). In this report, neuromodulation technologies like tDCS and TMS, with potential for rapid restoration of lost function, were listed among the main advances in recovery and rehabilitation since 2007; citing evidence that CNS neuromodulation may promote motor recovery particularly when combined with the patient's attempt to perform an impaired activity. The three top priorities were studies designed to 1) understand and harness clinical brain plasticity, 2) develop measures of neuroplasticity in the lesioned brain with relevance to important clinical outcomes, and 3) assess functional recovery and return to daily activities. Finally, the report stated that translating restorative post-stroke therapies should focus on matching the right patients with the right therapies. Our proposal addresses all of these objectives.

Gait Training. Improving the ability to walk is one of the primary goals of physical therapy treatments for individuals with a stroke, and walking speed can be predictive of level of disability. The ability to walk at speeds greater than 0.8 meters / second is predictive of the ability to walk freely in the community, walking at speeds of 0.4 – 0.8 metets per second is predictive of limited community mobility, while walking at speeds of less than 0.4 meters / second is indicative of being able to walk only in the home.[13] A recent review of gait treatment approaches has demonstrated improvements in gait speed when different methods of training are performed; however, not all individauls post stroke are able to improve walking ability and gait velocity to a level allowing community mobility.[14] We aim to enhance the beneficial effects of gait training with tDCS.

tDCS is an inexpensive and readily available device that can be used to facilitate stroke recovery by inducing changes in brain plasticity [15]. In tDCS, a constant current stimulator, with surface electrodes, provides a steady flow of low voltage, direct current (e.g., 0-4 mA) across the scalp and underlying brain tissue. Current shifts the resting membrane potential towards hyper or depolarization. The direction of the current determines its' effect on brain excitability (figure right). Anodal tDCS increases, and cathodal tDCS decreases the excitability of cortical tissue for periods of time that outlast stimulation for about 30 to 90 minutes. When switched on, the stimulator produces a transient tingling sensation under the



A tDCS set up showing active (C3) and reference electrodes (CSO). Current flow from C3 to CSO subjects tissue under C3 to anodal stimulation that increases cortical excitability. Reversing the current subjects C3 to cathodal stimulation that decreases cortical excitability.

electrode which fades in 30 to 60 seconds. An advantage of tDCS is that sham stimulation can be achieved without detection, simply by turning the stimulator off after the initial sensory experience. Prolonged effects of tDCS are attributed to persistent bidirectional modification of post-synaptic connections similar to those described for long-term potentiation and long-term depression effects[15]. Functionally, tDCS can improve performance on both sensorimotor and cognitive tasks in normal subjects [16]. In stroke patients, a recent meta-analysis of 8 studies on the effects of anodal tDCS has shown benefit for upper extremity motor recovery [17]. One study used TMS-evoked recruitment curves to measure cortical excitability [18] and found that improved hand function correlated with increases in cortical excitability. Whereas few studies have used tDCS to improve lower extremity function in stroke patients [19]; one study found that anodal tDCS applied to the lesioned hemisphere enhanced voluntary control of the paretic ankle [20] and our preliminary study found tDCS-induced improvement in gait velocity and physical function in patients with chronic stroke (see preliminary results below).

Hypothesized mechanism. Stroke damages brain tissue and it deafferentiates intact tissue in functionally linked regions both within and between hemispheres. Both factors alter cortical excitation and inhibition in neural networks that carry out motor functions [21, 22] and both can reduce a patient's capacity for increased cortical excitation [15]. We hypothesize that increasing cortical excitability with anodal tDCS prior to gait training will augment recovery.

Preliminary studies conducted by Dr. Mennemeier and the Investigational Team

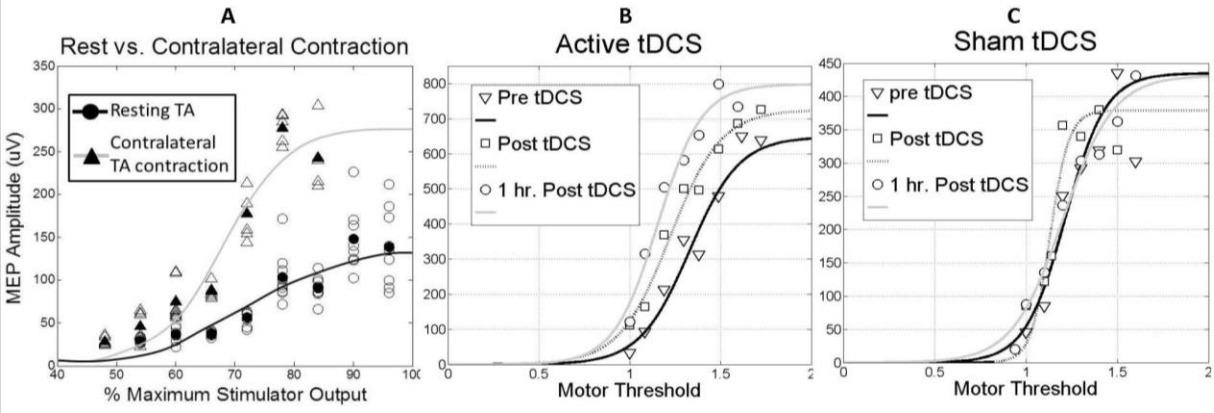


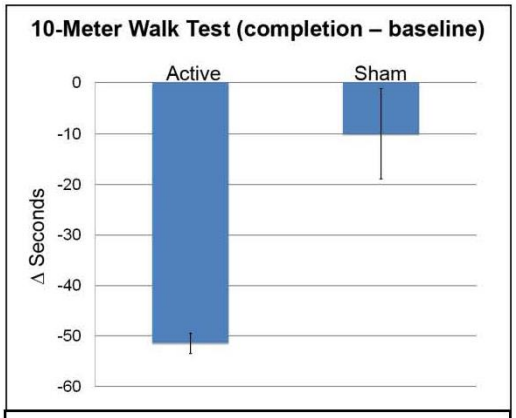
Figure A: recruitment curves for TA muscle obtained both at rest and during a 20% MVC of TA in the opposite leg. With contraction, the MT decreased from 67% to 58%of maximum stimulator output (MSO) and the max amplitude increased from 148μV to 277μV. **Figures B & C:** recruitment curves in figure **B** were obtained after anodal tDCS and those in figure **C** after sham tDCS. Curve slope steepens post-tDCS in **B** indicating increased cortical excitability but not in **C** following sham tDCS. The goodness of fit (r^2) exceeded 0.95 for all sigmoidal curves. The X axis is normalized to resting motor threshold.

Feasibility of obtaining valid TMS evoked recruitment curves for the TA muscle. In attempts to obtain recruitment curves for the TA muscle using a standard TMS coil, this study frequently exceeded stimulator output before the curve could become fully

established (i.e., plateau). In a series of normal subjects, this study overcame this limitation. First, by using a double cone coil which achieves deeper penetration of the magnetic field so TMS can be delivered at a lower intensity and, secondly, by having subjects make partial, isometric contractions of the TA muscle ipsilateral to stimulation (i.e., 20% of the maximum, volitional contraction: MVC). Contracting the ipsilateral limb enhances MEPs recorded from the contralateral limb (representative subject shown in Figure A, above). This method was then tested in normal subjects before, immediately following, and one hour after receiving active tDCS (10 minutes @ 1.4mA anodal) or sham tDCS delivered over motor cortex. (representative subjects shown in B and C). MEP maximums increased after active tDCS for up to 1 hr and the recruitment curves became steeper indicating a lower threshold (i.e., an increase in cortical excitability). Similar changes were not seen for sham tDCS. During testing of our initial participants with stroke we found this technique to work for only one of three individuals. We will thus attempt to establish a motor threshold over the lesioned brain hemisphere for placement of tDCS electrodes and to establish participant characteristics for the exploratory regression analysis. Then we will obtain recruitment curves from stroke patients' intact hemishphere – having them contract the non-paretic, ipsilesional TA muscle at 20% MVC while a recruitment curve is obtained for the non-paretic, ipsilesional TA muscle. Additionally, we will assess the responsiveness of MEPs from the ipsilesional TA muscle after the administration of anodal tDCS to the lesioned cortex during our baseline assessments.

Feasibility of using tDCS with treadmill training in chronic stroke.

In a pilot study investigating pairing locomotor training with transcranial direct current stimulation in patients with chronic stroke[23], our research collaborator at the University of Kentucky, Dr Sawaki, conducted a double-blind, randomized trial of active and sham tDCS (20 min at 2mA anodal stimulation over motor cortex) delivered just prior to locomotor training using a robotic gait orthosis treadmill. Eight participants (4 men, mean age=67.8; range=44-80) with chronic left hemisphere stroke (mean years post-stroke=4; range=1.1-11.6) were tested. Performance on a 10-meter walk test was the primary outcome measure, and assessments of functional ambulation category (FAC), timed up and go, balance, and the 16 item Stroke Impact Scale (SIS 16) were secondary measures. Improvement on the 10-meter walk test and the SIS 16 following active tDCS are shown in the figure - right. Active tDCS lead to greater improvement than sham tDCS on the FAC (p=0.028) and similar trends were evident for the SIS 16 (p=0.062) and the timed up and go test (p=0.066). This study shows that active tDCS augments gait training and function. The data were also used for power calculations.



The 10 M walk is completed faster after active tDCS (p=0.19).

Hypothesis and Specific Aims

Hypothesis: Increasing cortical excitability with active anodal tDCS prior to gait training will augment recover from a stroke.

Specific Aims:

1. Determine if active tDCS augments gait. Gait speed is a primary outcome measure. Spatiotemporal and kinematic gait assessment are secondary measures of gait. Over ground laboratory assessments of gait will measure 1) gait velocity and spatiotemporal gait measures using the GAITRite electronic walkway 2) ankle, knee, and hip angles using the SIMI motion analysis system. Changes in gait parameters will be expressed as difference scores from baseline. Difference scores will be compared between the active and sham groups to determine if tDCS augments gait parameters.
2. Determine if active tDCS augments cortical excitability after gait training. Cortical excitability will be defined by a cortical recruitment curve, a primary outcome measure, derived from plots of motor evoked potentials (MEPs) recorded from the ipsilesional TA muscle. MEPs are elicited by single pulse transcranial magnetic stimulation (TMS) delivered at increasing intensity over motor cortex. Changes in the slope of the recruitment curve signal change in cortical excitability. Difference scores from baseline will be compared between active and sham groups to determine if tDCS augments cortical excitability after FESAGT. A repeat fMRI will be performed to assess change in cortical excitability after gait training.

3. Determine if active tDCS augments physical function and social wellbeing. The Stroke Impact Scale-16 (SIS-16), a primary outcome measure, will be used to assess ADL/IADL, mobility, and social and occupational engagement at baseline and post treatment assessments. Difference scores from baseline will be compared between active and sham groups to determine if tDCS augments physical function and social well-being.

Exploratory Aim

Identify patient characteristics that predict response to treatment. Patients will be classified empirically based on their response to treatments. Regression analyses will examine whether and how initial impairment, functional level, and cortical excitability predict a treatment response.

Study Interventions

tDCS and gait training will be conducted at UCA three times a week for 4 consecutive weeks

tDCS. tDCS will be applied using a Soterix constant current stimulator with 5 x 5 cm ($25cm^2$) carbon rubber electrodes (Covidien 664 REFX 2x2) applied to the scalp with 10-20 conductive paste. The anodal electrode will be placed over the lower extremity representation of primary motor cortex of the lesioned hemisphere [established during TMS motor threshold testing (Baseline Testing) and the functional MRI assessment]. The cathodal electrode will be placed over the contralateral motor cortex. During anodal tDCS, participants will receive 20 min at 2mA over motor cortex (with 30 seconds of ramp-up and ramp-down). The highest current density for the electrodes is .08 (mA/cm^2) and and the total charge per session is 2.4 C. These values are well below the safety margins outlined in Nitsche [24]. During sham tDCS, current will be ramped-down and turned off after 30 seconds [25]. Both active and sham tDCS will be administered during the gait training protocol.

Table 1. Gait training protocol.

Phase *Sessions*	Gait training priorities	Treadmill Speed	Intensity	Manual Assistance
Phase 1 (1-6)	• Independence at the paretic leg • ▲ speed	0.8 mph minimum (goal of 1.4 mph)	Four 5 minute sessions	• As needed at trunk, paretic and non-paretic legs. • ▼ Assist to paretic leg.
Phase 2 (7-12)	• Independence at the paretic leg • ▲ speed	1.0 mph minimum (goal of >1.8 mph)	1b: ▲ session duration and ▼ number of sessions as tolerated	• ▼ Assist first to paretic leg, then to trunk/pelvis

Gait Training. Dr. Lairamore will supervise the gait training sessions. The gait training protocol is a modified version of the LEAPS protocol[26] where participants will be progressed from gait training phase 1 to a higher intensity of training in phase 2. All gait training will be performed on a treadmill and participants will wear a safety harness. Unlike the LEAPS protocol, participants in this study will not have a percentage of their body weight supported with the harness during gait training sessions.

Study Design and Procedures

Recruitment:

Stroke subjects will be recruited via advertisement and from participants in past stroke studies who indicated a willingness to be contacted for additional studies. We will recruit participants > 3 months post unilateral, stroke to minimize confounding effects of spontaneous recovery. Subjects who participated in previous versions of the study will be re-contacted if they indicated they were willing to be contacted for additional studies.

If they are willing to participate in the revised study they will be re-consented and re-enrolled under the new protocol.

Screening Procedures
All screening procedure will be conducted at either UAMS or UCA

For women of childbearing years a free pregnancy testing (urine dip stick test) will be required.

Administration of NIH Stroke Scale: administered and scored by study personnel who interview the participant. Severe language communication difficulties would preclude participation.

Administration of mofied Rankin Scale: administered and scored by study personnel who interview the participant.

Administration of TMS Adult Safety Screening (TASS, determine study eligibility): by study personnel.

Medical records will be reviewed to evaluate participant's study acceptability and to obtain clinical studies including neuroradiological imaging studies.

MRI procedures

Prior to the MRI scan, subjects may have a training session in the MRI simulator to help habituate and train them to the MRI environment. Per the MRI Policies and Procedures, the decision of who will be acclimated in the MRI Simulator will be made by the Research Coordinators and PI on a case-by-case basis. The PI for the study will have final say in this decision. Before the MRI scan, participants will be given an explanation of the study's procedures and screened with the MRI Safety Form for metal objects and claustrophobia. Participants will also be screened with the SAFESCAN® ferromagnetic detector according to MRI Policy and Procedures. The participant will then lie supine in the scanner. Participants will wear noise-cancelling headphones for communication and view visual stimuli through a mirror attached to the imaging head coil. Participants will undergo an anatomic scan to facilitate alignment of electrodes. Participants will also have a resting state scan in which they will be told to simply let their mind wander while they lay still in the scanner. Participants will also complete a scan measuring TA contraction. Subjects will be asked to contract the TA muscle in their right and left legs periodically depending on stimuli presented to them. Participants will have an identical repeat fMRI scan after completing the gait training protocol. Total scan time will be approximately 20-30 minutes per scan.

Randomization Procedures
After consenting, screening, and obtaining an MRI, participants will be block

randomized into groups (20 minute tDCS group + gait training or sham tDCS + gait training).

Baseline Procedures
The TMS motor threshold (MT) will be established [27] and the best location for eliciting MEPs from the contralesional TA muscle will be tracked on the subject's CT or MRI scan, or on a template MRI scan if clinical studies are not available, using Brainsight. Gait assessment (details provided in **Outcome Measures**) and the Stroke Impact Scale-16 will be performed for all participants at UCA. Motor evoked potentials and Recruitment curves (developed by the TMS procedure) will be performed at UAMS.

Intervention Procedures (Study Weeks 1 through 4)
Study interventions will be conducted 3 times a week for 4 continuous weeks. tDCS, and gait training will be performed at Movement Analysis Laboratory, Department of Physical Therapy, UCA as described above (**Study Interventions**).

Post-Intervention Procedures (Study Weeks 5(± 5 days) and 8 (± 10 days) :
During Study Weeks 1-5, and 8 Gait assessment (details provided in **Outcome Measures**) and the Stroke impact Scale 16 will be performed at UCA. During Study Weeks 5 and 8 TMS will be performed at UAMS and participants will complete a repeat fMRI scan. Details of TMS procedure used to establish recruitment curves are located in the Outcome Measures.

Reduction of Study Bias:
Dr. Lairamore will supervise delivery of interventions, and so, he will not be blinded to tDCS condition; however, Drs. Mennemeier and Garrison who collect and analyze data will be blinded to condition.

Study Locations:
tDCS, gait training,SIS-16, and the assessments of gait will take place in the Motion Analysis Laboratory at UCA; motor evoked potentials and recruitment curves developed from TMS are measured in the TMS and Human Electrophysiology core facilities at UAMS. Subject burden is reduced by requiring only four trips to UAMS over two - three months. (Subjects are informed that scheduling conflicts could result in an extra visit.) UAMS will be the IRB of record and Sponsor of the IDE.

Study Schedule

	Screening	Baseline	Study Weeks 1 -4 [b]	Study Week 5	Study Week 8
Consent	X				
Screening	X				
NIH Stroke Scale	X				
Modified Rankin Scale	X				
TASS	X				
Medical Record Review	X				
MRI	X			X	
Pregnancy Assessment	X				
Randomization	X				
Assessments					
Gait assessments		X	X	X	X
RC & SIS		X		X	X
Interventions					
tDCS			X		
Sham tDCS			X		
Gait training			X		

Definitions: TASS= Transcranial Magnetic Stimulation Adult Safety Screen, MRI=magnetic resonance imaging, RC & SIS-16=recruitment curve established using transcranial magnetic stimulation (TMS) and Stroke Impact Scale . [b]Three times a week for four weeks participants will receive active or sham tDCS and gait training interventions at UCA for a total of 12 treatment periods.

Study Population

Up to 100 stroke patients will be enrolled to obtain 88 who meet entry criteria and complete study procedures (i.e., 44 participants in each of the active or sham tDCS groups). Attrition, estimated at about 15%, will be handled by replacement.

Participants will be ≥21 years old to better represent the general stroke population. All participants will complete the NIH Stroke Scale, have evidence of gait impairment, and will be able to fully and safely participate in treatment.

Inclusion Criteria

- Stroke survivors > 3 months from most recent unilateral, stroke based on clinically or experimentally obtained MRI brain scans and behavioral evidence of stroke (e.g., risk factors, hemiplegia, unilateral sensory impairment, or localized higher cortical dysfunction) by report or in the medical record.
- Age: ≥21 years of age.
- Complete NIH Stroke Scale.
- Assements performed at screening include the following:
    - Sufficient endurance, motor ability and balance to ambulate at least 10

meters continuously with moderate or less assistance.

- Demonstrate a gait impairment during ambulation such as gait instability or inefficient gait pattern

- Pass the Transcranial Magnetic Stimulation Adult Safety Screen (TASS) except for items related specifically to stroke and the treatment for stroke, i.e., neurologic injury, having a seizure related to stroke, or having a crainiotomy for treatment related to stroke such as to relieve intracranial pressure.

Exclusion Criteria

- History of potentially fatal cardiac arrhythmias, such as ventricular tachycardia, supraventricular tachycardia, and rapid ventricular response atrial fibrillation with hemodynamic instability.
- Demand pacemakers or any other implanted electronic systems.
- Pregnant women, uncontrolled seizure disorder, Parkinson's Disease, Spinal cord injury, Traumatic brain injury with evidence of motor weakness, Multiple sclerosis.
- Documented episode in the medical record of a seizure occurring 1 month or more post stroke for which the patient received consultation or treatment for said seizure. Seizures occurring with in the first month following a stroke are not exclusionary unless followed by another seizure.
- Fixed ankle plantar flexor contracture, peroneal nerve injury at the fibular head as the cause of foot-drop.
- History of dementia, severely impaired cognition, communication or comprehension deficits.
- Presence of severe or frequent headaches
- History of Botulinum toxin (Botox) injection to either of the lower extremities within the 3 month period preceding study entry.
- Have other medical conditions or are taking medications that compromise ambulation or balance.
- Failure to meet established screening criteria for TMS or tDCS (i.e., TASS - except as noted under inclusion criteria)
- Principal Investigator's or Medical Monitor's discretion not to include a participant

Additional Exclusion Criteria for MRI Scan

- Claustrophobia, or the inability to lie still in a confined space
- Major medical disorders (e.g., HIV, cancer)
- Medications which may affect image quality (e.g., water pills)
- Magnetic metallic implants (such as screws, pins, shrapnel remnants, aneurysm clips, artificial heart valves, inner ear (cochlear) implants, artificial joints, and

vascular stents), as these may heat, pull, or twist in the strong magnetic field of the MRI scanner
- Non-removable dental implants, such as braces or permanent retainers, as these will distort the MRI images we collect (note: filings, crowns, and silver or gold teeth are OK)
- Permanent makeup or tattoos with metallic dyes
- A positive pregnancy test (for females), since the effect of strong magnetic fields on the developing fetus remains unknown and inconclusive. (We will conduct a pregnancy test for all female participants on the day of the MRI scan.)
- Psychotic disorders (e.g., schizophrenia)
- Any other condition that the investigator believes might put the participant at risk

Outcome Measures

Study Aim 1: Gait analysis (Dr. Garrison). Over ground laboratory assessments of gait: 1) Gait velocity and spatiotemporal gait parameters will be measured with the GAITRite system (CIR Systems, Inc., Havertown, PA) [28-35]. 2) Hip, ankle, and knee angles during gait will be measured using the Simi Aktisys gait analysis system (Simi Reality Motion Systems; Postfach, Unterschleissheim Germany). LED markers are placed on the participant's lower extremity. Ankle, knee, and hip angle data is obtained simultaneously to evaluate motor strategies for overcoming gait impairments. Both types of data will be collected simultaneously as participants walk 10 meters across the GAITRite walkway at a self-selected speed for 5 repetitions.

Study Aim 2: Recruitment curves. A Magstim 200 super rapid2 stimulator with a 110 mm double cone coil will deliver stimulation. First, the TMS motor threshold (MT) will be established [27] and the best location for eliciting MEPs from the contralesional and ipsilesional TA muscle will be tracked on the subject's MRI scan in Brainsight. EMG will be recorded from the TA muscles of both limbs. The MT will be determined by placing the TMS coil over the cortical motor area and delivering single pulses of increasing intensity until the optimal area of stimulation is found. Threshold will be defined as the percentage of the maximum stimulator output necessary to elicit a motor evoked potential (MEP) of 50 μvolts recorded from the tibialis anterior muscle of the contralateral leg in 3 of 6 stimulus trials. Motor thresholds for both the lesioned and non-lesioned brain hemispheres will be recorded.

Second, recruitment curves will be obtained as follows: 1) delivering ten, single TMS pulses beginning at 70% of MT, 2) increasing TMS intensity by 10% and repeating the process up to 160% of the MT or until a plateau in the recruitment curve is reached, 3) offline data processing will be performed with the Matlab curve fitting toolbox and 4) the

threshold, slope, and MEPmax, and the goodness of fit (R^2) will be calculated. A change in the slope of the recruitment curve will indicate change in cortical excitability.

Study Aim 3: Functional and social assessments. The Stroke Impact Scale-16 (SIS-16, completed by study team) is a standardized instrument [36-38] that assesses 3 functional domains in stroke patients including ADL / IADL, mobility, and social and occupational engagement.

Compensation

Participants will be remunerated $200 for completing the entire study protocol. They will be remunerated $75 dollars for partial completion.

Risks

A potential risk for study participation is the potential loss of confidentiality. Measures to protect the confidentiality of study participants will implemented as described in the Data Handling and Recordkeeping section below.

Device Risks:

Potential risks associated with tDCS include the following:

- A weak electrical current is applied to the brain via the scalp during tDCS using two surface electrodes. Current evidence shows that tDCS applied to motor and non-motor areas according to the present tDCS safety guidelines produces only minor adverse effects in healthy humans and patients with varying neurological disorders. One published safety study of tDCS, using stimulation parameters similar to this study, evaluated 103 subjects [25], and found no adverse effects on cognitive and psychomotor measures, nor EEG changes during or after 20 min of treatment. In a double-blind, sham-controlled study [39] it has been shown that comparing tDCS and sham stimulation of the motor cortex elicited minimal discomfort and difference in the duration of tingling sensations. Another study summarized adverse effects of 567 tDCS sessions over motor and non-motor cortical areas (occipital, temporal, parietal) in 102 subjects who participated in tDCS studies [40].
    - **active** tDCS intervention causes a sensation of mild tingling and itching under the electrodes that lasts for 10 to 30 seconds. Less frequently, a burning sensation or a burn is reported. Headache, visual sensations, difficulty concentrating, nervousness or overexcitability during procedure, unpleasant sensations, dizziness, fatigue, insomnia, and nausea are infrequently reported after tDCS. Because 10-20 conductive paste is

added to the electrodes to deliver tDCS, subjects will get paste in their hair.

- Risk will be minimized by the following steps:
    - First subjects are fully informed of all risks during the informed consent process.
    - For tDCS we use stimulation parameters that are well below the maximum levels that are considered safe. We will ensure there is no skin breakdown or lesions in the vicinity of electrode placement. The electrodes have connectors on their back to eliminate the possibility of contact with scalp which could cause a burn. We monitor electrode impedances during stimulation to ensure good conductance of current to scalp.
    - For TMS, we use stimulation procedures that fall within the guidelines recommended at the conclusion of the NIH Panel on TMS (see Wasserman [41]). Patients will be fully informed of the possibility of seizure, the plan for care in event of a seizure, and any foreseeable financial or medical consequences resulting from a seizure.
    - All subjects will wear ear plugs during testing sessions. TMS will be stopped if an ear plug falls out during a session.
    - A study physician trained in rescue procedures, will be on call when a subject is receiving single pulse TMS in this study. The study physician will be called by study personnel in the event of muscle contractions persisting after TMS (possible seizure) or complaints of dizziness, nausea, shortness or loss of breath, or loss of consciousness (possible syncope). Study personnel will note body parts that might be affected (e.g., the left arm or leg after right hemisphere stimulation) and/or other symptoms that might occur and report them to the study physician. [Should these be observed, the session will be terminated, and the subject will not be tested again].
    - If a subject were to have a seizure or syncopal episode during or immediately following TMS, the following precautions will be performed by study personnel:
    - The stimulator will be stopped and the coil will be removed from the subject's head.
    - The subject will be supported to physically guard against injury.
    - The subject will be placed on his/her side on a flat surface away from sharp edges.
    - The study physician will be called.
    - Emergency services will be called by study personnel to transport the subject to the emergency room if so directed by the study

physician.
- Emergency services will be called if the study physician cannot be reached.
- Either the study physician or the PI or subinvestigators will accompany the subject to the ER and explain the recommended post-event assessment which is as follows:
- It is recommended that after the seizure is over, the subject will be examined thoroughly for injuries and a complete neurological exam will be completed. Routine studies, including calcium, magnesium, and prolactin, will be completed and urine will be sent for a drug screen. An MRI scan of the head will be performed to rule out underlying epileptogenic pathology. An EEG will be performed with hyperventilation and anterior temporal leads. The subject will be advised that following a seizure provoked by TMS, the likelihood of further spontaneous seizures is not significantly increased unless other pathology is discovered. The subject will be scheduled for a neurology consultation. The subject will not be allowed to drive himself/herself home. Transportation would be arranged for the subject.
- The PIs and study physician would provide documentation that the seizure happened during a TMS session, that it does not constitute epilepsy, and that seizures caused by TMS have not resulted in future seizures. Seizures induced during electroconvulsive therapy (ECT) for depression, for example, do not cause driving privileges to be revoked in the state of Arkansas. Like ECT, a seizure occurring after TMS would not cause driving privileges to be revoked.

Potential risks concerning MRI scan: One potential safety concern is participant internal metal during MRI scanning, which can be painful and dangerous. Screening procedures administered prior to the scan will be used to rule out any participants who may potentially be at risk for harm as a result of internal metal objects. Another potential risk involved with imaging procedure is claustrophobia. Participants are able to quit the scan at any time by indicating to the technician that they wish to do so.

Other risks:

Potential risks associated with TMS must be considered in light of the duration and frequency of stimulation [41]. Most of the risks which are listed below have been associated with repetitive TMS subjects in this study ARE NOT RECEIVING REPETITIVE TMS. Rather, subjects in this study are receiving single pulses of TMS. Single pulses delivered in the fashion described above involve significantly less risk and discomfort than repetitive TMS (rTMS) where 100s to 1000s of pulses are delivered in succession. Adverse events rarely associated with single pulse TMS would include the following: 1) Vasodepressor (neurocardiogenic) syncope is a common reaction to

anxiety and psycho-physical discomfort. Syncope may occur more often than seizure during TMS testing and treatment and suspected seizure associated with TMS might actually be syncopal episodes rather than seizure [27] 2) Animals have shown permanent increases of the auditory threshold after high intensity single-pulse TMS [42] and humans have shown transient increases. Subjects wear earplugs to protect hearing during TMS. 3) Human subjects have rarely experienced seizure following single pulses of TMS [27]. In two cases, they were not healthy, normal subjects. In one case, the seizure may have been associated with brain lesions due to multiple sclerosis and with the use of olanzapine. In the second case, seizure was associated with the use of chlorpromazine and lithium and a family history of epilepsy. As mentioned above, a seizure or syncopal episode occurred during single pulse TMS in one normal subject who did not have identifiable risk factors for seizure or syncope [43]. A study physician experienced in TMS will be on call in case of an adverse event. A thorough plan is in place to contact emergency services if necessary and to follow up if a subject went to emergency services. Subjects are fully informed of risks during the informed consent process.

Risk factors that pertain to TMS studies (but have greater relevance to rTMS than single pulse TMS) are listed below. These risk factors are assessed via the TMS adult safety screen and the exclusion/inclusion criteria for this study.

- **Likely:** Subjects may feel anxious about participation. Subjects may experience minor discomfort associated with scalp muscle twitching.
- **Less likely:** Head pain related to stimulation of underlying muscle and nerves occurs in approximately 10% of subjects. The incidence and severity is a function of stimulus site and intensity. The symptoms are typically limited to the time of stimulation and can be treated with minor over-the-counter analgesics if necessary.
- **Rare:** The following have rarely been identified with TMS:
    - Syncope (as described above).
    - Seizure induction represents the most serious known risk of rTMS [41]. Seizures have been reported more frequently in subjects with brain lesions (e.g., stroke) but have rarely been reported in subjects with no history of seizures or neurologic disease.
    - Single pulse TMS has been associated with seizure in two persons who had risk factors for seizure such as taking medications that lower the seizure threshold and having a relative with epilepsy. One normal subject who did not have risk factors for seizure and who was not taking medication either had a seizure or a syncopal episode during a single pulse TMS study[27, 43].
    - A seizure caused by rTMS could place subjects at financial risk secondary to cost of medical care. Having a seizure might also influence driving privileges, employment, and the ability to obtain

insurance. Subjects are informed of these risks in the consent process.

- Effects on Cognition: Few adverse effects of rTMS on cognition have been reported [44] and there is a trend for performance to be better on measures such as delayed story recall. Using rTMS, two studies, reported possible adverse effects lasting up to one hour. Greenberg et al. (cited in Wasserman [41]) reported that task switching was impaired after 20-Hz stimulation of the right compared to the left dorsolateral frontal lobe [45]. Flitman et al [46] reported a significant decrease in logical memory one hour after testing after extensive stimulation using parameters that exceed guidelines for inter-train interval (150 trains of rTMS at 15 Hz, 750 msec duration, and 1.2 times the MEP).
- Effects on Mood: Dysphoria with crying has been induced after left prefrontal stimulation [47]. In contrast, high-frequency stimulation of the right prefrontal cortex may transiently improve mood as rapid-rate rTMS has been shown to be a safe and effective treatment in patients with depression.
- Effects on Hearing: Foam earplugs were effective in avoiding changes in the auditory threshold in a safety study of TMS [44].

Protection Against Risks: Repetitive Transcranial Magnetic Stimulation

Transcranial magnetic stimulation will be delivered by fully trained study personnel.

The following steps will be taken to minimize the risks discussed above. Additionally, subject exclusion criteria should eliminate subjects for whom risk is greater.

1. First subjects are fully informed of all risks during the informed consent process. We use stimulation procedures that fall within the guidelines recommended at the conclusion of the NIH Panel on TMS (see Wasserman [41]). Patients will be fully informed of the possibility of seizure, the plan for care in event of a seizure, and any foreseeable financial or medical consequences resulting from a seizure.
2. All subjects will wear ear plugs during testing sessions. TMS will be stopped if an ear plug falls out during a session.
3. A study physician trained in rescue procedures, will be on call when a subject is receiving single pulse TMS in this study. The study physician will be called by study personnel in the event of muscle contractions persisting after TMS (possible seizure) or complaints of dizziness, nausea, shortness or loss of breath, or loss of consciousness (possible syncope). Study personnel will note body parts that might be affected (e.g., the left arm or leg after right hemisphere stimulation) and/or other symptoms that might occur and report them to the

study physician. [Should these be observed, the session will be terminated, and the subject will not be tested again].

4. If a subject were to have a seizure or syncopal episode during or immediately following TMS, the following precautions will be performed by study personnel:
    a. The stimulator will be stopped and the coil will be removed from the subject's head.
    b. The subject will be supported to physically guard against injury.
    c. The subject will be placed on his/her side on a flat surface away from sharp edges.
    d. The study physician will be called.
    e. Emergency services will be called by study personnel to transport the subject to the emergency room if so directed by the study physician.
    f. Emergency services will be called if the study physician cannot be reached.
    g. Either the study physician or the PI or subinvestigators will accompany the subject to the ER and explain the recommended post-event assessment which is as follows:

It is recommended that after the seizure is over, the subject will be examined thoroughly for injuries and a complete neurological exam will be completed. Routine studies, including calcium, magnesium, and prolactin, will be completed and urine will be sent for a drug screen. An MRI scan of the head will be performed to rule out underlying epileptogenic pathology. An EEG will be performed with hyperventilation and anterior temporal leads. The subject will be advised that following a seizure provoked by TMS, the likelihood of further spontaneous seizures is not significantly increased unless other pathology is discovered. The subject will be scheduled for a neurology consultation. The subject will not be allowed to drive himself/herself home. Transportation would be arranged for the subject.

The PIs and study physician would provide documentation that the seizure happened during a TMS session, that it does not constitute epilepsy, and that seizures caused by TMS have not resulted in future seizures. Seizures induced during electroconvulsive therapy (ECT) for depression, for example, do not cause driving privileges to be revoked in the state of Arkansas. Like ECT, a seizure occurring after TMS would not cause driving privileges to be revoked.

Benefits

Potential benefits to subjects participating in the study include the following:

- The potential benefits to participants include personal satisfaction knowing

they have helped further research that could benefit patients with stroke and education about research studies.

- Further stroke patients could benefit from the treatment intervention in terms of increase ambulation and social well-being.
- Participants are not guaranteed a benefit from this study.

Data Safety and Monitoring

Data safety and monitoring will be performed in two ways. First, independent study monitoring will be performed by the Research Support Center at UAMS after the first 1-2 participants are enrolled. Thereafter, independent study monitoring will be performed by the Research Support Center at UAMS. Monitoring would occur according to the RSC monitoring plan. The Data and Safety Monitoring Plan describes operating procedures that will be in place to monitor compliance, study data validity and integrity, participant safety, individuals and/or entities (e.g., IRB) that will be involved in monitoring these procedures, and the frequency/regularity of this monitoring.

Adverse Events

Eliciting and Reporting Adverse Events:
Subjects will be monitored for the occurrence of adverse events throughout the study procedures.

Adverse Events Reporting and Evaluation:
All adverse events occurring during the course of the clinical study, whether device-related or otherwise, will be recorded on the Adverse Event CRF. For all adverse events, the study physician will provide an assessment of the adverse event, its treatment and resolution, and its relationship to the investigational device. All adverse events will be reported to the Sponsor and/or IRB in accordance with applicable institutional and federal regulatory guidelines.

Identification of Adverse Events:
An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered device-related.

Relationship of Adverse Events to the Study Device:
The study physician will assess the relationship of the adverse event to the investigational device. The relationship will be assessed using the following categories:

- Definitely Related: A direct cause and effect relationship between the investigational device and the adverse event exists.

- Possibly Related: A direct cause and effect relationship between the investigational device and the adverse event has not been clearly demonstrated, but is likely or very likely.
- Unlikely Related: A direct cause and effect relationship between the investigational device and the adverse event is improbable, but not impossible.
- Unrelated: The adverse event is definitely not associated with the investigational device.

Unanticipated Adverse Device Effects:
An unanticipated adverse device effect is defined as "any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with, a device; if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or application (including supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."
In the event unanticipated adverse effect occurs, the investigator will report the event(s) according to federal and institutional policies.

Serious Adverse Events:
Each adverse event will be assessed for its seriousness using the criteria outlined below. The term serious adverse event is not synonymous with a "severe" adverse event, which may be used to describe the intensity of an event experienced by the subject. An adverse event will be classified as serious if it meets any of the following criteria:

- Results in, or contributes to, a death
- Life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event, but it does not include an event that, had it occurred in a more severe form, might have caused death)
- Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure)
- Requires in-subject hospitalization or prolongs hospitalization
- Necessitates medical or surgical intervention to preclude a permanent disability or incapacity
- Results in a congenital anomaly or birth defect

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

Severity:
Each adverse event will be assessed for its severity, or the intensity of an event experienced by the subject, using the following.

- Mild: Discomfort noticed, but no disruption to daily activity.
- Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- Severe: Inability to work or perform normal daily activity.

Anticipated Adverse Events and Pre-existing conditions:

Pre-existing conditions will not be reported as an adverse event unless there has been a substantial increase in the severity or frequency of the problem which has not been attributed to natural history.

Data Handling and Recordkeeping

Each subject's name, birth date, address and phone number will be obtained for purposes of follow-up. We will ask for each subject's drug use history, medical history, and current drug use. Experimental data and questionnaire data will be collected. This information will be coded into the Microsoft Excel. Each subject's personal information will be de-identified in the database by using codes comprising the subject number and date and time the subject was tested. The PIs and study personnel at UAMS and UCA will have access to subject identities in order to arrange follow-up and to call them as part of the research project, such as follow-up contact. If subjects prefer e-mail correspondence research personnel will send e-mails for scheduling, follow-up, and research-related communication.

Data Analysis

Aims 1-3. Difference scores from baseline will be calculated for each outcome measure. A mixed model ANOVA with group (active tDCS groups versus sham tDCS) as the between subjects factor and time of assessment (pre, weeks 1-4, & one week andone month post) as the within subjects factor will be used to test all aims. A significant group effect, with active tDCS > sham tDCS, for any of the outcome measures would indicate that anodal tDCS augments gait training. A significant main effect of time would be evaluated using planned contrasts where we expect post treatment assessments to be improved relative to baseline. Interim analyses will be completed at critical stages during the protocol.

Power analysis: We aim to determine whether tDCS can augment the beneficial effect of gait training. Our preliminary study using tDCS to improve gait velocity and the SIS16 score yielded very large effect sizes for walking speed (2.95) and the SIS16 (1.32). In real terms, patients who received active tDCS reduced their time to walk 10 meters by about one minute (this could shave 5 minutes off a task, like getting mail, so it is functionally significant); whereas those who received sham reduced their time by only 10 seconds. Power calculations indicate that sample sizes = 11 will yield power of .95 and .80, respectively, to detect a tDCS-induced improvement gait velocity and physical function. However, assuming a very large effect size of greater than 2 is likely unrealistic. Therefore, we based our power analysis on determining a substantial meaningful change in gait speed (0.1 m/s) as determined by Perera et al.[48] Using a 2 x 3 mixed MANOVA with interaction and an estimated effect size of (cohn's d =

0.39)[37], a conservative r = 0.60[49] and an alpha of 0.05 we will need 37 subjects per group to achieve a power of 85%. Therefore, we set our sample size at 88, so our study has sufficient power to detect meaningful changes in gait speed for individuals with chronic stroke.

We set our primary study sample size at 88, so our study has sufficient power to detect a benefit of gait training and to determine if tDCS augments improvement.

Exploratory Aim. We will classify patients as "likely responsive" and "likely unresponsive" to tDCS based on the magnitude of difference scores and compare them to determined patient characteristics that predict a treatment response. Predictors for 88 subjects include 1) NIH Stroke Scale score, 2) initial levels of impairment, 3) initial MT of the contralateral TA muscle (and recruitment curve parameters form the ipsilateral TA muscle), 4) initial SIS-16 total and subscale scores, 5) stroke laterality, and 6) modified Rankin Scale scores. A series of regression analyses will be conducted to reduce the overall number of predictors and to build an initial model, which assess the predictive value or weight of remaining variables, and to cross-validate predictors. To determine which stroke related variables are associated with a response to treatment, brain lesions will be mapped onto templates and analyzed using lesion subtraction techniques with the public domain MRIcro and MRIcron software programs (see Core B). Lesion subtraction will identify the lesion sites that are common to treatment responders and not common to nonresponders.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The PI or designated staff will discuss the informed consent form with the subject volunteer. The consent process will take place in a quiet and private room. Subjects may take as much time as needed to make a decision about their trial participation and may take the document home if desired. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and follow-up requirements of the study. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. No research related procedures will be performed prior to obtaining informed consent. All signatures and dates will be obtained. A copy of the signed consent will be given to the participant. The informed consent process will be documented in each subject's research record.

Vulnerable populations: Stroke patients can have cognitive deficits that could render them vulnerable. Patients for this study will not be entered if there is evidence of preexisting dementia or if they exhibited language comprehension or other cognitive deficits that precluded understanding of instructions or of the informed consent.

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant. This study will be registered on http://www.ClinicalTrials.gov.

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