Cover Page

O+icial Title: Brain Networks of Turning Performance with Aging and Stroke

NCT Number: NCT05475236

Document Date: 10/13/2022

Protocol

1. Project Title

Brain Networks of Turning Performance with Aging and Stroke

2. Investigator(s):

Clayton W. Swanson, PhD
David J. Clark, ScD
Dorian Rose, PhD
Damon Lamb, PhD

3. Abstract:

The objective of this study is to examine the neural control of turning while walking, which is often impaired for older adults and people who have had a stroke. **Leveraging the infrastructure of Dr. David Clark's IRB approved ongoing Merit Review study called the CONTROL Study (IRB201803010 - *Cerebral networks of locomotor learning and retention in older adults*) this study adds one additional (optional) assessment visit to measure brain function using transcranial magnetic stimulation (TMS) which is a form of non-invasive brain stimulation.** The CONTROL Study collects multiple forms of turning performance data in older adults; however, the it does not perform or collect transcranial magnetic stimulation (TMS) data to assess excitatory and inhibitory neurophysiological function in motor networks of the brain.

Recent work demonstrates significant associations between brain excitatory/inhibitory function and turning performance in older adults, although these results remain largely preliminary. Therefore, **the objective** of this proposal is to further elucidate associations between neurophysiological function (measured with TMS) and measures of turning performance. **Specific Aim 1** will test the hypothesis that greater cortical inhibitory function will be associated with faster turn speed and shorter turn duration for 360˚, 180˚, and 90˚ turns. **Specific Aim 2** will test the hypothesis that greater cortical inhibitory function will be associated with greater segmental turning strategies (i.e., head leads in the turn followed by shoulders, trunk, etc.) of the axial skeleton. **Specific Aim 3** will test the hypothesis that participants with greater baseline cortical inhibition will demonstrate larger 360˚, 180 ,˚ and 90˚ turning performance gains. This pilot study will enroll 40 mobility compromised older adults and 10 participants post-stroke which will provide preliminary data for a future grant submission, proposing a larger scale clinical trial of turning rehabilitation for mobility compromised adults.

4. Background:

Gait and balance impairments during straight ahead walking are well documented in older adults and post-stroke survivors, but rarely is turning factored into either the assessment or intervention. Nearly all tasks performed throughout the day require some amount of turning. In fact, people over the age of 65 execute between 300-1500 turns per day. Even with the abundance of turning in daily life, there remains a relative paucity of research targeted to understanding age and stroke related turning deficits, or the potential for achieving turning improvements following an intervention. Recent research has documented significant differences in 360˚and 180˚turning performance between neurotypical young and older adults, such that older adults were found to turn more slowly and to have a reduced peak velocity. Moreover, our recent research as shown that compared to conventionally measured straight

ahead walking variables (i.e., walking speed), performance on the 360˚turn test provides excellent ability to discern between neurotypical middle-age and older adults. This finding indicates that turning ability may be more sensitive to lower limb motor control differences between these populations. Similarly, stroke related research demonstrates increases in the duration and number of steps needed to complete 360˚turns.

We propose to use transcranial magnetic stimulation (TMS), which is a non-invasive brain stimulation technique to measure motor cortex neurophysiology during a single study visit . Specifically, we are interested in three measures associated with inhibitory activity respectively termed the cortical silent period (cSP), short interval intracortical inhibition (SICI), and long interval intracortical inhibition (LICI). These measures represent inhibitory activity, specifically gamma-aminobutyric acid (GABA) which is the primary inhibitory neurotransmitter in the brain. Although there are certain unique features for each of these measures. Specifically, the cSP is a single pulse TMS measure which assesses GABA-B corticospinal inhibitory activity while both SICI and LICI are paired pulse TMS measures which are thought to measure cortical (rather than corticospinal) levels of inhibitory activity. Moreover, the two paired pulse TMS measures assess different GABAergic subtypes. Specifically, SICI measures GABA-A activity while LICI measures GABA-B activity. Notably, my prior research is the first to demonstrate associations between the cSP and turning performance for older adults, such that those older adults with greater levels of inhibition (i.e., longer silent periods) demonstrate better turning performance (i.e., shorter turn duration). Although the precise mechanism linking cortical inhibition to turning performance remains unclear, there is emerging evidence that motor cortex inhibition predicts performance on tests of motor response-inhibition (i.e., the termination or prevention of movement). In the context of turning (e.g., 90˚, 180˚, and 360˚turns), response-inhibition may help facilitate transitioning away from “automatic” straight ahead walking allowing for neuromuscular control to initiate a change in direction. This concept has been demonstrated for other complex walking tasks, such as obstacle avoidance or sudden step length adjustments. Together, these results indicate that cortical inhibition likely plays an important role in gait related performance. However, no research has assessed all three inhibitory measures and their associations to turning performance. Moreover, no studies have assessed whether baseline levels of motor cortex inhibitory activity are predictive of turning performance gains or tDCS induced neuroplastic alterations.

5. Specific Aims:

The specific aims are developed around the premise of incorporating turning data collected from the CONTROL Study and incorporating those data with the unique TMS data collected from this study.

Specific Aim 1: Determine the extent to which cortical inhibition is associated with 90˚, 180˚, and 360˚ turn duration and velocity in older adults.
Hypothesis 1: Greater levels of cortical inhibitory activity will be associated with shorter turn duration and faster peak turn velocity for 90˚, 180˚, and 360˚ turns.

Specific Aim 2: Determine the extent to which cortical inhibition is associated with segmental turning strategies in older adults.
Hypothesis 2: Greater levels of cortical inhibitory activity will be associated with greater degrees of segmental specific turning strategies for 90˚, 180˚, and 360˚ turns.

Specific Aim 3: Determine the extent to which cortical inhibition is predictive of turning performance changes post-intervention.

Hypothesis 3: Participants with greater cortical inhibitory activity at baseline will demonstrate larger improvements on the 360˚and 180˚turn tests.

6. Research Plan:

Study Overview

This study will recruit zero participants.

- Please refer to Table 1 outlines what measures will be shared from the CONTROL Study and which measures are unique to the current study.

Table 1: Shared and Unique methods and metrics between the CONTROL Study and this study.

	Approved via Dr. Clark's CONTROL STUDY	Unique to my study	Risk Category	Use of Biodex Chair
Methods and Metrics				
- Turning measures (90˚, 180˚, 360˚)	X		Greater than Minimal Risk	
- Locomotor intervention and "performance gains"	X		Greater than Minimal Risk	
- Short form 36 (questionnaire)		X	Minimal Risk	
- Katz (questionnaire)		X	Minimal Risk	
- cSP (TMS measure)		X	Greater than Minimal Risk	X
- SICI (TMS measure)		X	Greater than Minimal Risk	X
- LICI (TMS measure)		X	Greater than Minimal Risk	X
- Maximal Voluntary Contraction		X	Minimal Risk	X
- Electromyography		X	Minimal Risk	

Participant Screening

Recruitment will coincide with the CONTROL Study. Specifically, participants will be screened by the CONTROL Study staff to determine if they meet the study criteria. This includes participants between the ages of 65 – 95 years for the older adult participants and 65 – 85 for the post-stroke participants. The exclusion criteria include participants who have contraindications to non-invasive brain stimulation (i.e., TMS). This would include having metal in the head, a pacemaker, a wound on the scalp, or a history of seizures. Additionally, medications affecting the central nervous system including, but not limited to, benzodiazepines, anti-cholinergic medication and GABAergic medication will be exclusionary as they could influence the results of TMS.

Informed Consent and Onsite Screening Visit

Participants will undergo informed consent for the CONTROL Study and at that time will be invited to undergo an additional informed consent for this study. Prior to the participant signing the additional consent form research staff will explain the TMS study protocol to participants. For participants who wish not to participate in the TMS visit they may continue with the CONTROL Study protocol.

At the discretion of the Principal Investigator, any individual may be deemed ineligible for further participation in this study if there are concerns about the individual's capability to perform study procedures or if it may be unsafe for the volunteer to participate in the study.

Transcranial Magnetic Stimulation (TMS) Visit

Various assessments of muscle strength, neural control, and health and independence will be made during the TMS assessment visit. These assessments include:

Maximal Force Assessment

Participants will perform a series of maximal voluntary contractions (MVCs) to determine the maximal tibialis anterior strength output for each leg. On separate trials, participants will be encouraged to produce as much force during a dorsiflexion as possible with each tibialis

anterior muscle. Once force output for subsequent trials is within 10% the largest force producing trial will be recorded and used during the cSP TMS trials.

Electromyography (EMG)
EMG electrodes will be placed on each tibialis anterior muscle which will be used to measure muscle activity during the TMS trials. Please see the section Transcranial Magnetic Stimulation below for more information.

Transcranial Magnetic Stimulation (TMS)
Prior to starting TMS, participants will first complete a TMS safety screening questionnaire. The answers to this safety screening will be reviewed and approved by the researcher performing TMS and/or the PI. Like figure 1 but on the tibialis anterior muscles rather than the vastus medialis oblique's participants will have two surface EMG electrodes placed on each muscle belly and one on a boney landmark (e.g., patella). Participants will be seated in the TMS chair. Then research staff will measure the participants head to locate the center. This is completed by identifying the middle points when measuring from the nasion to inion and from tragus to tragus. Once the center of the head is determined we will measure laterally 1 cm on both cortical hemispheres this point will denote the starting spot for stimulation. After locating the general location, the research staff will work to identify a more precise location for stimulation by incrementally increasing the stimulation intensity and systematically moving the TMS coil around until stimulation results in a consistent muscle response. Once an initial muscle response is observed stimulation intensity will be determined to consistently generate an appropriate muscle response and amplitude. This procedure will be conducted on both cortical hemispheres.

Figure 1: Example of TMS participant set up

Following the determination of location and intensity for stimulation the tibialis anterior muscles, the 6 TMS trials will be performed at random. Each of these trials will be roughly three minutes in length and will include collection of the cortical silent period, short interval intracortical inhibition, and long interval intracortical inhibition for each hemisphere independently.

Questionnaires
We will administer two questionnaires aimed at assessing self-reported measures of health and independence when performing activities of daily living. Both are short, simple, paper-based questionnaires. Specific examples include:

- Short Form-36 – is a set of 36 questions aimed at assessing self-reported measures of health.
- Katz Index of Independence – is a set of questions aimed at assessing one's level of independence when performing activities of daily living.

Possible Discomforts and Risks:

There is a risk that participants may find the questionnaires uncomfortable or embarrassing if they feel uncomfortable with their answers. In an attempt to alleviate these feelings participants may skip any question that they do not wish to respond do.

Falls. While we do not anticipate a fall occurring there is the potential that a participant could fall while getting into or out of the Biodex seat (Figure 1). To mitigate this risk the Biodex seat rotates and lowers. Additionally, study staff will be present to help participants safely navigate their body position into the seat. Once seated, participants will be securely harnessed in (similar to a seatbelt in a vehicle).

Headache. Although rare, the most common side effect from TMS brain stimulation is headache. However, individuals should not, participate if they have a history of migraine or other types of severe or frequent headaches. It is also possible that participants may experience some neck stiffness or neck pain. This is believed to be due to the straight posture of the head and neck we will require during the experiment.

TMS is a safe, non-invasive brain stimulation technique that can be used for both diagnostic and therapeutic procedures. The single and paired pulse TMS techniques that will be performed in this study have been used extensively in thousands of research studies and on tens of thousands of subjects in the United States and around the world. Single and paired pulse TMS techniques are considered very safe when accepted guidelines are followed, and no long-term risks have been reported involving the use of single and paired pulse TMS. For most people, the stimulation is not painful, but occasionally slight discomfort or headache can occur. The headaches go away quickly with nonprescription medication. TMS produces a clicking sound when a current is passed through the stimulation coil. During repetitive TMS stimulation this click can result in ringing in the ear and temporary shifts in your ability to determine the pitch and loudness of sounds if no protection is used. Hearing damage is possible, and one subject suffered permanent hearing damage when hearing protection fell out, although this was done using repetitive TMS (rTMS). This study does NOT include rTMS and only single and paired pulse TMS will be employed in this study. Animal and human studies have shown that earplugs or headphones can effectively prevent the risk of hearing disturbance due to TMS. Therefore, participants will be fitted with earplugs during TMS. If individuals find the procedure too uncomfortable, they may discontinue at any time.

TMS can interfere with implanted medical devices and will not be done in people who have pacemakers, implanted pumps, or stimulators, such as cochlear implants or in people who have metal objects inside the eye or skull (dental work such as fillings and similar procedures do not pose a risk and are acceptable). If participants have an implanted device or metal object that is not safe for TMS, they will not be allowed to participate.

In general, the risks associated with TMS are very minimal, but research has shown that there is a very small risk of seizures if repetitive TMS (rTMS) is done with very intense, high frequency stimulation or with trains of stimulation separated by a second or less. Such intensity, frequency, and repetition rate will not be used in this study as the study does NOT include rTMS and only single and paired pulse TMS methods will be employed. Finally, there is no medical risk associated with the surface EMG recordings of the muscle responses to TMS.

8. Possible Benefits:

There is no direct benefit to the participant.

9. Conflict of Interest:

None.

10. Statistical analysis and sample size calculations

For each aim, the objective of this pilot study is to calculate variance of response and confidence intervals of effect sizes to be used as preliminary data for a future grant submission which will incorporate a clinical trial for turning specific rehabilitation. The proposed sample size of 50 per group for the older adults is considered sufficient for providing stable and reliable estimates of variability and effect size. The proposed sample of 10 stroke participants will allow for the assessment of feasibility.

Data and Safety Monitoring Plan

Adverse Event Reporting

Adverse events will be reported according to the guidelines of the University of Florida Institutional Review.

Reporting within 5 days of the PI becoming aware will apply to adverse events that meet all of the following criteria:

- Serious
- Unexpected
- Related or the Relationship is “more likely than not”

Adverse events will be added to the cumulative event table and reported at continuing review when they meet either of the following criteria:

- Serious (but expected) and related or the relationship is “more likely than not”.
- Unexpected (but not serious) and related or the relationship is “more likely than not”.

A *serious adverse event* is any adverse event that results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolonging existing hospitalization,
- a persistent or significant disability/incapacity,
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when the event may jeopardize the patient or subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

An *unexpected adverse event* is any adverse event that is not consistent with the current investigator brochure, protocol, consent form, or is not part of the normal disease progression. In addition, known adverse events may occur more frequently than expected. If so, then this meets the definition of “unexpected” and must be reported to the IRB.

Protection Against Risk

Staff training: All personnel will be thoroughly trained in the study procedures by the Principal Investigator or other appropriate member of the research team and will complete all required trainings concerning human subjects research at the University of Florida.

Health monitoring and medical response: Volunteers at risk of health problems due to recent history of medical conditions (e.g., serious cardiac or pulmonary conditions) will be excluded, as noted above in the inclusion/exclusion criteria. Any adverse events will be recorded and monitored as required by our University of Florida Institutional Review Board. In the event of a medical emergency at the VA Hospital (our study site) we will call the hospital emergency

response line, 6-9-1-1 and alert them to a code blue (medical emergency). Subjects will be able to terminate a study session at their request at any time without prejudice. Minimization of risk during neurorehabilitation and assessments will be accomplished by monitoring vital signs, with prescribed criteria for termination of the testing session. Vital signs will be monitored before, during and after assessment. Contraindications for participation will include resting heart rate >100 bpm or <50 bpm, resting systolic blood pressure >180 mmHg or <100 mm Hg or resting diastolic blood pressure >100 mmHg. Indications to terminate physical activity will include subject complaints of shortness of breath, light-headedness, dizziness, confusion, severe headache, dyspnea or onset of angina. If any of these conditions are greater than mild or persist after rest, the patient's primary physician will be called and patient referred for evaluation. If the patient complains of angina at rest, loss of consciousness occurs, or cardiac arrest, emergency medical services through 911 will be called immediately. Portable defibrillators are available.

Confidentiality: Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Confidentiality of data will be maintained by using research identification numbers that uniquely identify each individual. Safeguards will be established to ensure the security and privacy of participants' study records. Appropriate measures will be taken to prevent unauthorized use of study information. Data other than demographic information will not use names as an identifier. The research ID number will be used. The research records will be kept in a locked room in the study site. The files matching participants' names and demographic information with research ID numbers will be kept in a locked file that uses a different key from that of all other files. Only trained and certified study personnel will have access to these files, and they will be asked to sign a document that they agree to maintain the confidentiality of the information. Electronic records will be stored on password protected network server maintained by the university information technology department. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we access personal health information and medical records only after receiving signed informed consent.

TMS Safety: Our protocol uses stimulation parameters that are considered standard practice for single- and paired- pulse TMS. These parameters have been used safely in thousands of prior research studies. The most common side effect of TMS is a headache. To minimize risks associated with TMS, participants will complete a pre-TMS screening form and will be monitored throughout the stimulation session. Additionally, participants will be asked to report any discomforts. If stimulation is or becomes uncomfortable, the stimulation levels will be decreased to a comfortable level or will be stopped.

Questionnaire administration: Questionnaire data are collected in secure spaces where the interview cannot be overheard. Participants will be informed that they are not required to answer questions that they do not wish to answer.