Official Title: Development of Mechanistically Informed Therapy for Task-Specific Dystonia Using Noninvasive Neuromodulation

Protocol#: Pro00094131

NCT#: NCT06422104

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DUHS IRB Application (Version 1.31)

General Information

*Please enter the full title of your protocol:		
Development of Mechanistically informed Therapy for Task-Specific Dystonia Using Noninvasive Neuromodulation		
***Please enter the Short Title you would like to use to reference the study:**		
Neuromodulation Therapy for Task-Specific Dystonia * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

The overarching goal of this study is to develop a non-invasive neurostimulation therapy for patients with focal hand dystonia (FHD). Specifically, the data obtained from this study will determine if engaging the striatum during non-invasive brain stimulation in the form of Transmagnetic Stimulation (TMS) can provide prolonged improvement of dystonic symptoms. Previous work in this field has advanced our understanding of regional brain circuit disruptions in dystonia and shown some efficacy in improving focal dystonia using non-invasive brain stimulation, though as of yet the effects are relatively modest and not enduring.

Goal:To characterize baseline behavioral and structural differences between focal hand dystonia subjects and healthy volunteers and evaluate safety and feasibility of neurostimulation therapy.

Visit 1:70 FHD subjects and 70 healthy volunteers (HV) will be recruited to provide writing samples on digital writing tablet at Duke Brain Stimulation Research Center (BSRC).

Visit 2: A small cohort of 70 FHD subjects and 70 HV from visit 1 will be recruited to undergo functional MRI brain at Duke Brain Imaging and Analysis Center (BIAC). Data from visit 2 will also be used to localize the cortical target for TMS stimulation in visits 3, 4 and 5. Overall, data from visits 1 and 2 will be used to establish baseline outcome measures for visits 3, 4 and 5.

A urine drug screen and pregnancy test prior to visits 3-5.

Visit 3, 4 and 5: 5 HV who completed visits 1 and 2 will be recruited to undergo development of TMS stimulation protocol at Duke BSRC. TMS Stimulation will be provided up to 20 minutes (at 10Hz) with a writing sample during stimulation. Subjects will also perform a writing assessment before and after each stimulation block. An fMRI will be performed after completion of each TMS stimulation session.

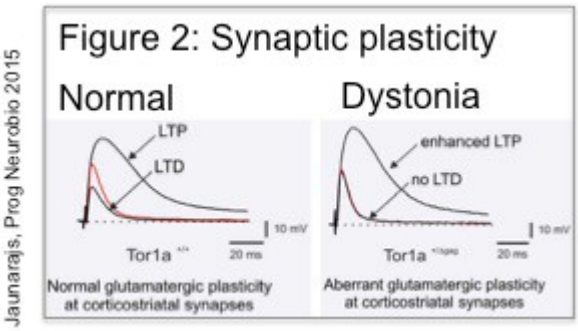
20 focal hand dystonia subjects who completed visits 1 and 2 will also be recruited to undergo 3 visits of TMS stimulation at Duke Brain Stimulation Center. The 3 visits will each be 1 week apart. 2 visits will involve active TMS and 1 visit will be sham TMS. During one of the active TMS visits, TMS coil will be applied to the premotor cortex for brain stimulation while during the other active TMS visit, TMS coil will be applied to the primary sensory cortex. TMS stimulation protocol will consist of 10Hz stimulation for up to 20minutes with a writing task during the stimulation block. Subjects will undergo a writing assessment before and after each stimulation block and complete TMS side effects survey. Writing task is different from writing assessment in that writing task will only be used as part of the investigational therapy while writing assessment will be data collected for outcomes measures. fMRI will be performed after completion of each of the 3 TMS visits.

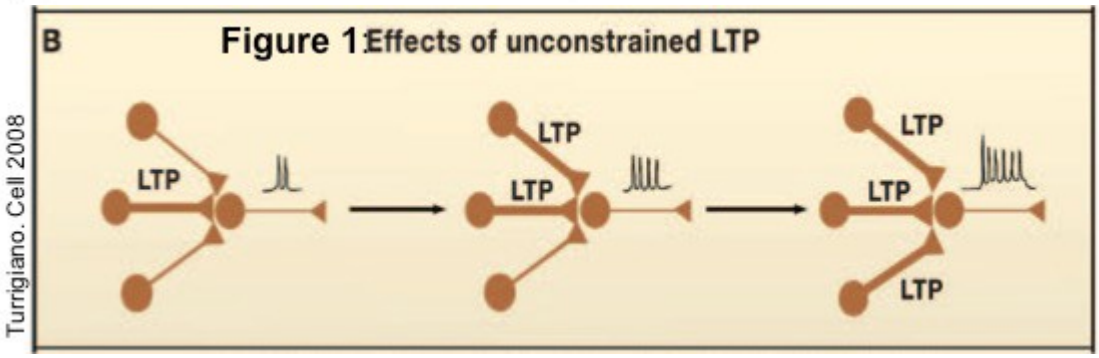
Writing assessment, TMS side effects and fMRI data from the 3 visits will be used to evaluate safety of TMS stimulation protocol and feasibility of writing task during stimulation protocol.

Background & Significance

- Should support the scientific aims of the research

Dystonia is an involuntary movement disorder characterized by sustained or intermittent muscle contractions causing abnormal postures that are patterned and associated with overflow of muscle activation(1). Writer's cramp is characterized by excessive, unintended muscle activation selectively occurring during the task of writing. Its prevalence is 6.9 per 100,000 persons. Thirty percent of subjects report economic problems and 21% report pain significantly impairing independence in activities of daily living and work(1–3). Currently no disease modifying therapies are available. Most effective symptomatic therapies include botulinum toxin to transiently paralyze the overactivated muscles. Such treatments require access to highly specialized practitioners to avoid causing impaired dexterity, exhibit waning effects over the 3-month treatment interval, and vary efficacy based on the complexity of an individual's dystonic movements. For WC subjects, the risk of invasive brain surgery modalities such as Deep Brain Stimulation is weighed against the severity of their symptoms and DBS therefore is rarely a viable option (4). As a result, there are currently no highly effective non-invasive treatment for writer's cramp. Improved efficacy, longer therapeutic duration, and ultimately curative therapies for writer's cramp dystonia are needed.





Converging lines of evidence from human subjects and rodent models of dystonia suggest that abnormal striatal plasticity appears to be a common feature(5–8). In normal healthy mice, the presence of long-term potentiation (LTP) and long term depression (LTD) leads to normal plasticity of excitatory corticostriatal synapses. In dystonia, alteration in striatal physiology is characterized by abnormal plasticity of enhanced LTP and absence of LTD at excitatory corticostriatal synapses in a DYT1 mouse model(9). In addition, last year one of my mentors Dr. Calakos' laboratory discovered that hypoactivity of a translational regulatory pathway was shared across three forms of dystonia, two inherited dystonias and one sporadic focal dystonia(10). The pathway, eIF2alpha, had been previously described to regulate the threshold for establishing long term synaptic plasticity(11). The eIF2 alpha pathway impairments in dystonia predict excess LTP and impaired LTD, consistent with the DYT1 model observations.

Based on these mechanistic findings as well as clinical observations(6), we view dystonia as a syndrome of abnormal synaptic plasticity and circuitry. We hypothesize that dystonic muscle activation beyond those intended for motor task are due to an imbalance in the circuit towards synaptic strengthening. Bidirectional plasticity is a necessary and conserved feature that allows co-activated cells to strengthen connections and non-correlated circuits to be extinguished. Deleterious effects of unopposed synaptic strengthening can be easily imagined, and one specific circuit manifestations modeled in Figure 1. Over time, unconstrained LTP will lead to loss of circuit specificity and may

generate the overflow of muscle activation found in dystonia. According to this model, therapeutic strategies restoring LTD may enable appropriate weakening/pruning at non-task specific synapses and lead to better motor control.

Therefore, a mechanism-based neurostimulation paradigm for dystonia would aim to restore LTD in striatum. In rodent models of dystonia, 10Hz stimulation for 5 minutes at cortical afferents produces long lasting depression at medium spiny neurons in striatum(12). Interestingly, 10hz TMS stimulation paradigm for up to 50mins has been applied in 4 human research studies to demonstrate engagement of striatum(13–16). There is also a requirement for a dopamine-dependent "pausing" of cholinergic interneuron firing for LTD to occur in medium spiny neurons in striatum(17). However, in rodent models of dystonia, dopamine signaling has been found to increase, rather than decrease, activity of cholinergic interneurons. Administration of the anticholinergic drug, trihexyphenidyl, an established therapy for dystonia, in these mice rectifies the abnormal activation of cholinergic interneurons and restores LTD(18–22). In humans, administration of trihexyphenidyl to spasmodic torticollis patients transiently rectified functional dystonic brain activity on fMRI(23). Thus, I hypothesize that a 10Hz rTMS protocol combined with anticholinergic treatment will enable LTD plasticity.

For specificity, stimulation will be delivered in a cortical region previously implicated in the writing network. Performance of the task in the stimulation protocol may help optimize the plasticity refinement to strengthen intended circuits and extinguish unintended actions.

TMS is a non-invasive neuromodulation strategy that has shown some benefit in WC patients. TMS involves a short intense current in a coil applied over the scalp to generate a magnetic field which then passes through the skull and induces an electric field that, depending on frequency of stimulation can depolarize or hyperpolarize local cortical neurons(24,25). A key feature of the current proposal is that I will improve upon previous applications of TMS in dystonia by targeting the deep brain region of striatum, as opposed to superficial cortex; and do so in a way that may be sufficient to induce long-term synaptic plasticity responses. I hypothesize that focal TMS stimulation designed to induce LTD in WC dystonia will improve decreased striatal activity on fMRI. To test this hypothesis, I will dose TMS using knowledge of brain circuitry in dystonia. A key parameter for effective dosing of TMS is the specific brain region to target. The striatum is a deep brain tract that is not directly targetable by TMS. However, stimulating cortical regions with TMS in a manner that affects projection neurons (as opposed to intra-cortical circuits) provides access to striatum.
Fortunately, in dystonia and WC, much work has been done to define relevant cortical inputs to striatum (25–34).

Prior research demonstrates 2 cortical regions that can be targeted by TMS to affect striatal activity in WC subjects. One potential cortical target is premotor cortex. In primates, radioactive tracer injected at premotor and motor cortex demonstrated direct projection of premotor cortical axons to striatum, particularly putamen(35,36). Studies in WC using *in vivo* tract tracing suggest the premotor to putamen pathway is impaired(37).

Furthermore, a meta-analysis of5 TMS studies in WC dystonia subjects also demonstrated consistent albeit short-term benefit when TMS was applied at premotor cortex supporting its role in engaging dystonia brain circuitry(38–43) and supporting the idea that these regions are also linked by a common connection. A second potential cortical target is primary sensory cortex. Previous connectivity analysis in WC subjects demonstrated decreased functional connectivity between putamen and primary sensory cortex(27). Among the previous studies applying TMS to WC subjects, the study that showed the longest benefit (2weeks) targeted the primary sensory cortex(44). In this study, TMS stimulation will be applied to the premotor cortex during one visit and to primary sensory cortex during another visit to evaluate the optimal cortical target for modulating putamen activity using TMS in WC subjects.

Design & Procedures

- Describe the study, providing details regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

Consent process and data collection will occur in a private room at the Duke Morreene Road Clinic or Duke brain Imaging Center or Duke Brain Stimulation Center in Red Zone of Duke South. All subjects

will sign an electronic single consent form uploaded to redcap or a printed hard copy. Any subject who wishes to sign their consent forms virtually, a blank consent form will be shared with subjects by redcap or emailed to them prior to the virtual visit. A phone or video visit will then be scheduled. At the virtual visit, an IRB approved study script will be used to review the research study with them for consenting purposes. The subject can then sign the consent form on redcap electronically or mail the signed hard copy to the study staff. The signed consent form will then be scanned and uploaded to Oncore and maestro care. Subjects can opt in or out of visits 2, and 3-5 of the research study.

Visit 1: 70 HV and 70 FHD subjects will be recruited at the Duke BSRC in the Duke Main Hospital. After the study team consents the subject, the following will be obtained: Patient's medical history to evaluate appropriateness of
dystonia diagnosis. Patient will also be asked about the symptoms and signs of dystonia on rating scales including Adult dystonia and disability rating scale (ADDS)(45) Burke Fahn Marsden Rating Scale (BFM) and Pain Scale.

Subjects will then be asked to perform 3 writing samples (WT-1, WT-2, and WT-3) and non-writing samples on a digital tablet. WT-1 will be a single sentence written repeatedly 10 times to quantify writing performance. WT-2 will be a different single sentence written 10 times. WT-3 will be a linguistically diverse paragraph. All writing tasks will be performed by subjects using their dominant **l eft or right hand**. All subjects will be videotaped from the neck down, focused on their arms and hands during the writing sampling to allow careful examination of subject's hand and finger movements for Writer's Cramp Rating Scale (WCRS)(46) by 2 expert physicians (one Duke physician and one external physician) blinded to the group identity.

The patients videos of writing assessments are reviewed by the research team to ensure no personal identifier information (face, name, DOB) is visible. Videos are then deidentified and an ID number is assigned to each video for blinding purposes. The research staff then imports the videos to a secure Duke server including DukeBox and Duke PACE environment. The external physician will only access the videos using the Duke PACE environment while the internal Duke physician may access the videos using either the Duke Neurology server, DukeBox or Duke PACE environment. The physicians will rate the participants' writing assessments using established dystonia rating scales (WCRS, BFM).

Visit 2: 70 FHD subjects and 70 HV from visit 1 will be recruited to undergo a functional MRI brain at Duke BIAC. To assess patient's baseline, subjects will copy a sentence using their dystonic **left or right hand** in fMRI suite alternated by periods of rest using an MRI compatible digital tablet. Writing task and control motor task will be back-projected onto a screen located at the head of the MRI bed using an LCD projector. Subjects will view the screen via a mirror system located in the head coil. Task onset will be electronically synchronized with the MRI acquisition computer using Cigal computer software. Task administration and collection of writing data will be computer controlled. The scanning session will take about 1.5 hr and include structural MRI, DTI, Swan, resting state fMRI and task-based fMRI.

BOLD images will be acquired using a GE Premier Performance 3T MRI scanner, which is an improved version of GE's FDA-approved Premier system, but with better capabilities for high-resolution imaging. All operational parameters on this improved system will be within FDA guidelines to meet the same minimal risk device criteria and ensure safety of human subjects. As such, an Investigational Device Exemption (IDE) is not necessary. The research conducted under this protocol is not to evaluate the safety and efficacy of this device.

A urine drug screen and pregnancy test prior to visits 3-5.

Visits 3, 4 and 5: 5 healthy volunteers who completed visits 1 and 2 will be recruited to undergo development of TMS stimulation protocol at Duke BSRC. Following protocol development, 20 focal hand dystonia subjects who completed visits 1 and 2 will also be recruited to undergo TMS stimulation at Duke BSRC. All 25 subjects will undergo the procedure as detailed below:

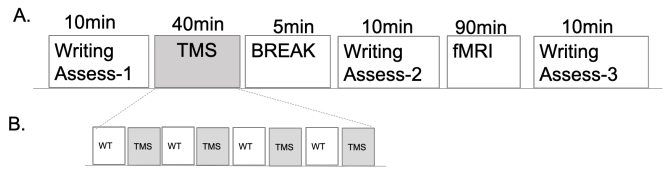


Figure 3: Sequence of events for research visits 3, 4, and 5. A) Overview of TMS stimulation, writing assessment and fMRI imaging. B) TMS session will be divided into 4 blocks of TMS stimulation at 10Hz alternated by 4 blocks of writing, each 5minutes.

1. MRI Brain images from visit 2 will be uploaded to a neuro-navigation system (Brainsight: Rogue Research, Montreal, Canada) at the Brain Stimulation Service Stimulation Service Center

(BSSC), a core facility in the Department of Psychiatry at Duke University. Each subject will be brought to the BSRC for TMS preparatory session. The goal of the preparatory session will be to identify TMS coil position on subject's scalp at premotor cortex, and primary sensory cortex and to measure the subject's motor threshold. To identify scalp location, each subject's head will be co-registered with his/her structural MRI in neuronavigation system. TMS will be performed with a figure–of-8 coil and a MagPro Stimulator (MagVenture, Denmark).

2. Motor threshold (MT) is defined as the minimum magnetic flux needed to elicit a threshold EMG response in a target muscle in 5 out of 10 trials. MT is the standard in the field for determining the intensity of rTMS for each individual to reduce seizure risk. The motor evoked potentials (MEP) for the contralateral first dorsal interosseus (FDI) will be measured with EMG. The scalp region producing the largest amplitude MEP will be identified. At that scalp location, the lowest TMS intensity able to elicit 5 MEP's of ≥50μV in peak-to-peak amplitude in 10 trials at this site will be determined, using a descending method-of-limits procedure initiated by the MUSC PEST program. MT will be determined for one or both hemispheres with the muscle at rest (verified by baseline EMG). Individual MT will be used to determine the intensity of stimulation for each individual, as recommended by safety guidelines.Each subject will then be acclimated to the sort of TMS pulses to be delivered with a series of single pulses at the target site.
3. Healthy volunteers will undergo TMS stimulation protocol development. Subjects will receive 10Hz active stimulation at premotor cortex during one visit and primary sensory cortex during another visit for up to 20 minutes with stimulation intensity up to 120% of resting motor threshold which is within the published safety guidelines (47) and based on previously published protocol used in multiple human studies(13–16). The resting motor threshold is a baseline stimulation intensity determined using the protocol in step 2. Additional stimulation parameters including duration of continuous stimulation, interstimulus interval, stimulation intensity, orientation of magnetic coil, biphasic or monophasic stimulation will be developed with healthy volunteers based on the published safety guidelines(47), writing assessment (includes writing and non-writing sampling) and feasibility within 20 minutes stimulation paradigm.
4. WC subjects will undergo TMS stimulation visits 3, 4 and 5. 2 visits will include active TMS stimulation while the remaining one visit will be a control sham stimulation. Of the 2 active TMS stimulation visits, subjects will receive TMS at premotor cortex during one visit and at primary sensory cortex during the other active TMS visit. The dosage of active stimulation will be 10Hz for up to 20 minutes with resting motor threshold up to 120% which is within the published safety guidelines (47) and based on previously published protocol used in multiple human studies(13–16). During both active and sham stimulation blocks, subjects will be asked to perform a writing task of writing a diverse paragraph as an online stimulation task. The stimulation block will be preceded and followed by a writing assessment and TMS acute side effects survey to assess safety of the stimulation. Visit 3, 4, and 5 will occur 1 week apart. Subject will undergo fMRI after each of the 3 TMS visits.
5. Of note, although both writing task and writing assessment will comprise of a writing and non-writing sample on a digital tablet, writing assessment will additionally entail video recording of the subjects' writing from the neck down, focused on subjects' arms and hands. These recordings will be used to complete Writer's Cramp Rating Scale (WCRS)(46) and Adult dystonia and disability rating scale (ADDS)(45) by an observer blinded to treatment.Overall, writing task is different from writing assessment in that writing task will only be used as part of the investigational treatment while writing assessment will consist of outcomes measures data collected for analysis.
6. Data from visits 3, 4 and 5 will be used to determine safety of TMS stimulation protocol and feasibility of writing task and fMRI with stimulation protocol.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Inclusion criteria:

Healthy Control Participants:

1. 18yrs and older
2. **Left or Right hand dominance**
3. Age-matched to Focal Hand dystonia patients
4. Must be able to sign informed consent

5. Must be literate

Focal Hand dystonia Patients:

1. 18yrs and older
2. **Left or Right hand dominance**
3. **Diagnosed with Writer's Cramp dystonia in left or right hand**
4. Must be able to sign informed consent
5. Must be literate

Exclusion criteria:

Healthy Control Participants and Focal Hand dystonia Patients (visit 1)

1. Other neurological movement disorders diagnoses including other types of dystonia, Parkinsonism, or essential tremor
2. Botulinum toxin injections within 3months of research study
3. Medications with effects on the central nervous system including anticholinergic, benzodiazepines, and muscle relaxants among others within 1 week of the study
4. No physical or occupational therapy of the upper extremities

Healthy Control Participants (visits 2-5) and Focal Hand dystonia Patients (visits 2-5):

1. Other neurological movement disorders diagnoses including other types of dystonia, Parkinsonism, or essential tremor
2. Botulinum toxin injections within 3months of research study
3. Medications with effects on the central nervous system including anticholinergic, benzodiazepines, and muscle relaxants among others within 1 week of the study
4. No physical or occupational therapy of the upper extremities
5. Any contraindications to MRI (ie: metal in body or implanted medical devices, etc)
6. Any contraindication on TMS adult safety screening (TASS form) including seizure history, pregnancy, brain injury, cranial metal implants, known structural brain lesion

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

For focal hand dystonia patients, the study team will review subjects with either ICD9 code 333.84 or ICD 10 G24.9 code in the online query DEDUCE to generate a list of potential study candidates. These patients will then be contacted directly by one of four means:

1) telephone using a telephone script 2) personal email provided in their electronic medical record 3)Duke mychart messaging 4) written letter to their home address. As per Duke's policy, three attempts will be made to contact patient after which it will be assumed that patient is not interested in the research study.

Additional contact approaches will include contacting the patient's primary provider who can then reach out to the patient to notify them of this research study. To ensure subject selection is equitable and all relevant demographics groups have access to study participation, study fliers (a writer's cramp study flier and a healthy subject study flier) will be posted on clinic announcement boards in patient areas of Duke Movement Disorders clinic, Neurology and Movement disorders clinics, physical and occupational therapy clinics, and Orthopedic hand clinics in the state of North Carolina.

The study team will email the research flyer and research study brochure to these locations so that they can be posted or distributed and also email Dystonia research foundations and Dystonia support groups in neighboring states. The study team will also give engage Dystonia support groups in nearby states and provide information about the study using an IRB-approved presentation. The powerpoint presentation submitted with this IRB application is the presentation I would give to patients in the Dystonia support groups to help with raising awareness about the study. I have added language that is highlighted on page 8 of the IRB protocol to describe this additional recruitment material. The study team will also post the study flier information on the DukeList website under volunteers to recruit healthy volunteers for the study. We will have a waiver in place to handle any self-referral calls or emails.

All potential subjects with writer's cramp or healthy volunteers will be introduced to the study through the contact approaches listed above and if agreeable, will have an in-person screening by the study team during visit 1 at Duke Brain Stimulation Center at Duke Main hospital.

The study team will also review the clinic schedule in the Duke Movement Disorders Center for potential FHD subjects seen by Movement Disorders Specialist who meet the basic inclusion/exclusion criteria and have appointments that day. While recruiting FHD potential subjects, we may also introduce the study to caregivers who accompany the patient to the clinic and ask if they would also like to be part of the study and possibly enroll as a Healthy Control subject.

To recruit healthy subjects, BIAC's healthy volunteer registry will be also used and guidelines followed as indicated in their IRB Pro 00010672. We will also recruit healthy participants from Duke Clinical Research Unit Volunteer Registry and follow guidelines from their IRB Pro 00010672.

Subjects will be reimbursed $50 for each of the five visits. Subjects completing all 5 visits will receive a maximum of $250.

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Healthy control participants and Focal hand dystonia subjects should be capable of providing consent.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

Previously stated

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant women, prisoners or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what

available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

There are no known long-term health risks to the use of magnetic resonance imaging per se when operated within FDA guidelines. However there are safety concerns posed by the strong magnetic fields used to make images. All scans
conducted under this IRB protocol meet the FDA's guidelines for non-significant risk for static field strength, specific absorption rate (SAR), time varying magnetic fields (dB/dt), and acoustic noise.

There are no known long-term health risks to the use of rTMS per se when operated within consensus safety guidelines(47). The Duke Medical Center Institutional Review Board recently classified two similar research applications of rTMS
proposed by Simon Davis as a "non-significant risk" (Protocols 20218 and 24349). In 2008, the FDA approved the use of high frequency rTMS in the treatment of depression. Also in 2008, an international consensus conference on safety
guidelines for rTMS met, including former and current representatives from Duke Brain Stimulation Center (Drs. Lisanby and Peterchev). Their report(47) systematically reviewed the thousands of healthy subjects and patients who have
undergone rTMS in order to allow for a better assessment of relative risks. The relative infrequency of adverse events using rTMS was noted. They concluded that in the case of Class 3 studies (studies involving indirect benefit and low risk in normal subjects and patients that are expected to yield important data on brain physiology or safety, but have no immediate relevance to clinical problems), normal volunteers should be permitted to participate in rTMS research when it is
likely to produce data that are of outstanding scientific or clinical value. They also concluded that this research can be performed in a non-medical setting (i.e., psychology labs, robotics labs, research institutions, etc. as opposed to a hospital or appropriately equipped outpatient clinic). The Rossi et al. consensus report went on to suggest safety guidelines based on the now rather extensive international experience with rTMS(47). These guidelines include the rTMS intensity and
timing parameters considered safe, training, and planning for and managing emergencies. We will follow these guidelines, and have incorporated them into our screening and session procedures.

Safety of rTMS in dystonia patients: TMS has been used in a number of dystonia (focal hand dystonia, and cervical dystonia) patients (39–44,48–50). There have been no reports of serious adverse events with the use of rTMS in dystonia
subjects in all of the clinical studies reported to date. No seizures have ever been reported in normal adult subjects, when high frequency rTMS was administered within the established safety guidelines.

Participation is voluntary, and there will be no pressure or time constraints regarding the decision to participate. Healthy participants and dystonia patients may benefit from improvement in their writing task, monetary reward or
compensation, and good will of helping the progress of scientific research. The information learned from this study may aid our understanding of how the brain networks in dystonia patients are different from healthy adults. This knowledge
may lead us towards future therapy to improve different types of focal dystonia in adults.

MRI Adverse Events Plan:
An MRI procedure is considered to be "minimal risk" according to federal definitions. To date, no after effects have been revealed and the FDA has classified the MR procedure as possessing a "non significant risk" for the subject of study. To minimize risks, all subjects will be screened for metallic devices, implants and other contraindications to scanning. Women of child-bearing capacity will be excluded for pregnancy using a pregnancy test prior to scanning. Those unlikely to
tolerate the sense of confinement during scanning will also be excluded.

Adequate safety monitoring and observation during scanning will be provided, as will measures to enhance the subject's physical and emotional comfort during the scan. It is possible that some subjects might experience minor distress by the confined and noisy conditions in the scanner. This possibility will be minimized by earplugs and headphones, and experienced technicians who will monitor all subjects for distress. In the event that a subject becomes anxious during a scan,
the study will be halted. Subjects will be able to communicate with the investigators at all times using the intercom system should they wish to request that a study be terminated or have concerns or questions during the procedure. The
subject is in full view of the operator at all times.

The probability of an incidental finding that might lead to the diagnosis of an unknown abnormality is greater than zero. All subjects who undergo MR-related procedures will be alerted to this possibility during the consent process. In that

event, subjects or their designated physician will be provided copies of their anatomical scans and advised to seek further evaluation if they have concerns.

TMS Adverse Events Plan:
Seizure is a theoretical risk with rTMS. In the Rossi et al. report it was stated that "The occurrence of seizures has been extremely rare, with most of the few new cases receiving rTMS protocols exceeding previous guidelines, often in patients under treatment with drugs which potentially lowered the seizure threshold." As Rossi et al. delineate, "rare" means that 16 cases (out of tens of thousands of rTMS sessions over the last two decades) of seizure related to rTMS have been reported. Eight occurred before safety parameters were established in 1997. Of the other eight reports, six occurred either when the safe rTMS parameters were exceeded or other safety guidelines ignored, and the actual occurrence of a seizure has been questioned in the other two (i.e., convulsive syncope or pseudoseizure may have occurred). In a workshop convened by the National Institute for Neurological Disorders and Stroke (NINDS) in 1996 (Former Duke investigators, Dr. Luber, and Dr. Lisanby were participants)(51), researchers in the field agreed upon a set of *rTMS consensus safety guidelines*, including recommended stimulation parameters and contra-indications, and these consensus guidelines have been updated(47). Widespread adherence to the 1996 guidelines has resulted in the virtual elimination of inadvertent seizures in rTMS studies(47). The levels of stimulation used in this protocol are well within safety guidelines(47,51).

We will screen subjects for known risk factors for seizure with rTMS (medical screening and medical history). Personnel who administer rTMS are trained to recognize a potential seizure event and to act as "first responders" in order to administer appropriate initial care. All study personnel have undergone Basic Life Saving training, and seizure-specific training. The major physical signs the study personnel will look out for in detecting a potential seizure include chewing movements, convulsions/tremor/shaking, difficulty talking, a blank stare, eyes rolling up, and profuse sweating. If any of these signs are observed, study personnel will stop the research procedure and inquire whether the subject feels okay. If the subject is unresponsive (and therefore likely experiencing a seizure), first-aid will be supplied. The first-aid response consists of making sure the subject is physically safe for the duration of the seizure. This involves moving the subjects out of the rTMS chair and onto the floor lying down on his or her left side. The subject will be kept lying down on his or her left side, while the staff call emergency medical help, via a 911 call. Resources available in the laboratory include a first-aid kit and immediate phone access. A seizure constitutes a reportable adverse event, and will thus be immediately reported to the IRB via the Safety Events Form mechanism.

The most commonly reported side effect of rTMS is headache. This headache is typically of a muscle-tension type. It usually develops during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation, and usually responds promptly to single doses of over the counter pain medications. Neck pain or scalp pain may also occur. Both are usually managed easily with over-the-counter analgesics. Participants may take Advil or Tylenol to reduce discomfort. Tylenol or Advil will be used according to recommended dosage, ensuring that the participant has no allergies and has not taken other NSAIDS or acetaminophen. Liver damage can occur when more than 4,000 mg of acetaminophen are taken in 24 hours or when taken with alcohol. Ibuprofen can cause stomach bleeding in certain individuals or when not adhering to dosage recommendations. Once the Advil or Tylenol has had time to take effect, we will resume stimulation. If there is still discomfort, topical lidocaine cream may be applied to the area of the scalp where stimulation occurs. Topical lidocaine has been shown to relieve discomfort resulting from rTMS for some people. Topical lidocaine should not be used on large areas or on cut, irritated or swollen skin. Twenty minutes must be allowed for the lidocaine cream to take effect. If implemented, Tylenol, Advil, and lidocaine cream will be used as directed.

As noted in Rossi et al(47), Loo and colleagues reported mild and transient changes in auditory threshold in two depressed patients following a 2-4 week rTMS course of rTMS. Cases of tinnitus have been reported after rTMS treatments. In addition, recently in a study investigating the effects of rTMS on symptoms of depression, a patient experienced moderate to severe tinnitus after an rTMS session in which earplugs were not used. Rossi et al. recommended that hearing protection always should be worn during rTMS application, and that individuals with cochlear implants not receive rTMS. In the current study, earplugs will be worn by all subjects during rTMS procedures. Individuals with cochlear implants will be excluded from participation.

Illicit drugs such as cocaine can reduce the seizure threshold. As a result, all subjects will undergo urine toxicology test prior to each TMS session and positive subjects will be excluded from the study. Risks to the unborn children of

pregnant women receiving MRI and rTMS are unknown. Pregnant women will be excluded as per IRB policy. Female subjects are tested with a urine pregnancy test prior to every MRI session and TMS session as per IRB-approved BIAC policy. These female subjects agree not to become pregnant while remaining within the subject pool, and to notify the experimenter or subject coordinator if they become pregnant. If sexually active, the subject must agree to use appropriate
contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not
acceptable methods for routine use. If the subject has any uncertainty about whether they could be pregnant, another urine pregnancy test will be performed before they can participate in this protocol. The person(s) who will perform the
urine pregnancy test will have successfully completed training as directed by the Chair of Obstetric and Gynecology of the Duke University School of Medicine. The urine pregnancy test kits used for this research study will be those
commercially available test kit specified by the Chair of Obstetric and Gynecology and in routine use at DUHS.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There are no costs to the subject associated with this research.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

Writer's cramp behavioral data: Endpoints:Objective handwriting parameters of duration of writing, speed of handwriting, fluency of writing movements, axial pen pressure and interpretability of handwriting will be collected using a digital
tablet and a pressure sensitive pen for data analysis. Additionally, an observer blinded to subject group will complete Writer's cramp rating scale(46) and BFM Rating Scale from video recordings of subjects performing each writing task (WT-1, WT-2 and WT-3). At the initial visit, patient's medical history will be collected to evaluate appropriateness of dystonia diagnosis. Patient will also be asked about the symptoms and signs of dystonia on rating scales including Adult dystonia and
disability rating scale (ADDS)(45) Burke Fahn Marsden Rating Scale (BFM) and Pain Scale to compare their baseline symptoms before and after all 4 visits.

Sample Size justification: A review of prior research studies employing TMS in writer's cramp and healthy volunteers measuring handwriting showed statistically significant effect sizes of 15-20% on various measures of writing performance
using 6-12 subjects per group(38–40,43). A power analysis of our preliminary writing behavior data from 30 subjects in visit 1 demonstrated sample size of 60 in TMS for effect size of 30% with alpha = 0.05. Assuming that I will be able to
achieve similar sensitivity in writing metrics, I propose to study 20 patients in TMS group using writing task and fMRI as outcome measures for analysis (visit 1). Due to the pilot nature of fMRI and TMS stimulation parameters, the minimum
number of subjects needed to calculate statistical power were selected. Therefore, in order to reach pilot data set of 20 patients in TMS group with 31% screening failure rate, we need approximately 70 FHD subjects.
The 70 healthy volunteers will allow us to do a better statistical power analysis of clinical and fMRI outcomes measures to evaluate effect size for TMS As a result, we would like to increase our overall goal enrollment target to 140

Our preliminary analysis of the Duke patient population reveals sufficient population of FHD subjects to recruit for our study at Duke University. Our electronic patient database identifies 186 Duke patients with a specific diagnosis of organic
writer's cramp (ICD 9 code 333.84). Because ICD 10 code does not have a specific writer's cramp diagnosis, we suspect that more cases are included within the ICD G24.9 (focal dystonia) group. Therefore, the primary care providers for all 837 subjects with either of these codes may be contacted by research coordinator for patient candidacy for this research study as detailed in Section 6 eIRB submission form.

Analysis and Statistics: Michael Lutz, PhD in the Department of Neurology, **Alec McConnell and Hussein Al-Khalidi in the BERD core of the Statistics Department** will be **involved** the de-identified data **anal ysis** but will be not involved in collecting the data. Visit 1 data of handwriting metric differences between healthy participants and focal hand dystonia patients will establish writing metric sensitivity at our site and recalculate power analysis to adjust cohort sizes, or improve technique, as indicated for visits 2, 3, and 4. For Visit **3 -5**, a two-way ANOVA will be performed with groups (healthy vs dystonia) and stimulation type (task during vs after stimulation) as the main factor within subjects. A two-way repeated measures ANOVA will be conducted with stimulation type (task during vs after stimulation) and treatment type (sham vs active) as the main factors between subjects for each handwriting measure.

fMRI data*:* All image pre-processing will be implemented using the FSL program (https://wiki.biac.duke.edu/biac:fsl). Block design fMRI data will be extracted by time-series modeling using rectangular time windows for the motor task and rest periods. Group data will then be analyzed using GLM modeling. Any fMRI network identified in writing performance from previous fMRI research using the writing task in dystonia patients will be prospectively applied to the fMRI data of the
subjects. Specifically, the imaging data from the pre and post fMRI sessions will be log transformed and subtracted from each other at each site in each subject. The global mean across sites will be subtracted from each log-transformed regional value, producing regional values normalized to each subject's global mean activity. In a second normalization, the mean for each site across subjects will be subtracted from each regional value. The result of these two normalizations is a subject x region matrix with the mean activity within and across subjects removed. This will be cross-correlated with the patterns previously found in order to quantify pattern expression for individual subjects in the present group. These individual subject pattern expressions will be entered into regressions predicting brain performance in order to verify that the patterns predict performance in new group. In addition, pattern expression will be used to predict rTMS effects on writing task
performance (for example, differences in RT with active and sham rTMS).

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

Safety monitoring: The subjects will be fully informed of the nature of the study requirements prior to enrollment and periodically throughout the study. The subject's well being will be continuously monitored by the experimenter, and the

Principal Investigator will report all serious adverse events in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with the Center's

standard operating procedures.

The study monitor will be Dr. Bukhari-Parlakturk. Dr. Bukhari-Parlakturk will ensure the quality of the study and establish that each co-investigator and research team staff is complying with the investigational plan and IRB regulations.

Monitoring of this protocol is simplified by the fact that this study involves a small number of investigators and a single facility in which the study is being conducted.

Throughout the investigation, the monitor will ensure that the facilities being used continue to be acceptable for the purposes of the study, that the investigational plan is being followed, that any changes to the protocol have received IRB

approval and accurate, complete, and current records are maintained, that accurate, complete, and timely reports are made to the IRB. This will be accomplished through quarterly meetings during which the status of the protocol,

investigators, and IRB compliance are reviewed. The monitor will review each research chart for completeness and accuracy. She will confirm that inclusion and exclusion criteria have been met for each subject enrolled, and compliance with

all other aspects of the investigational plan are met. A report will be submitted annually to the IRB. Any instances of reportable events or unanticipated problems will be reported to the Duke University IRB as outlined in the IRB Policies and

Procedures.

Data Storage and Management: Research team members are expected to follow these major principles for data storage and management.

1) All research data are stored in Dr. Bukhari's lab folder on the Neurology server. This folder is periodically backed up onto the Dukebox research folder to generate 2 copies of all dataset with the exception of patient videos which are

maintained only on the Bukhari lab folder.

2) In order to give access to the 2 physicians to rate the writing assessments, deidentified patient videos are also uploaded to 2 additional secure Duke servers including DukeBox and Duke Pace environment.

3) Additionally, all data (raw and analyzed) files from Bukhari folder are regularly copied to a private lab database (administered by Neurology IT Dave Parrish) and accessible only to the Department Chair.

4) Study patient demographics, medical history and rating scales will also be stored in Duke Redcap database.

5) fMRI images and data will be stored on Brain Imaging and Analysis server (smb://munin3.biac.duke.edu) and data analysis performed and stored on the server.

6) Statistical tests and the statistical approach to be performed on the data must be arrived at in advance, must be appropriate and clearly stated. When feasible the approach should be arrived at in consultation with Michael Lutz, **Alec McConnell and Hussein Al-Khalidi**. Data dredging should be avoided by all investigators and discouraged by the PI

Research Integrity: All students, and research staff are responsible for maintaining a culture where all should feel free to voice their opinions as to the strengths and weaknesses of the research questions pursued, the methods used, and

the interpretation of results as outlined in the Department of Neurology Research SOP. Any concerns regarding data integrity should be brought immediately to the attention of the PI, Department Chair or departmental ethics ombudsman.

If for any reason, a research personnel is uncomfortable speaking with any of these individuals he/she may bring their concerns to the anonymous data integrity line in place in the Duke SoM at **1-800-826-8109**

Research Responsibilities: All students, and research staff are responsible for the documentation and preservation of all data generated in the process of performing research in the Dr. Bukhari's lab. In addition to being essential to the

generation of scientific knowledge, proper data management is a good research practice that ensures reliability and reproducibility in all our work. In addition, because the ultimate goal is for findings made in our research group to become

the basis for published scientific articles, it is of utmost importance that all source data used as the basis for any publication and materials used for grant applications to be deposited in a centralized location readily accessible to the PI and to

other members of the laboratory.

Research Training: Upon joining the Bukhari lab, the PI will meet individually with each student, and research staff to go over the expectations for laboratory work, including data management and research integrity in the laboratory. The

PI will go over best laboratory practices, archiving procedures, server space allocation and details of data maintenance. The PI will monitor data deposition on the servers and periodically will perform audits to ensure compliance with the

established SOP. The trainee and PI will co-sign that the proper training has taken place.