Clinicaltrials.gov Title:
Response Inhibition in Tourette Syndrome

NCT03628703

Latest version approved by IRB: 4/2/2020
Title below is the local IRB protocol title

I. TITLE: Preliminary Investigations of Transcranial Magnetic Stimulation (TMS) to understand Diseases and Disorders that affect the Motor System in Children

Version 23
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I. ABSTRACT

Automatic and purposeful movements require signaling from the brain and spinal cord (central nervous system - CNS) via the nerves (peripheral nervous system - PNS) to muscles. Abnormal input into this pathway from the basal ganglia or cerebellum results in disorders of movement regulation and coordination. Diseases of the brain and spinal cord (central nervous system) can lead to weakness. Motor pathways can be assessed through testing of clinical properties of movement, such as strength, bulk, tone, reflexes, movement regulation, and coordination. Motor pathways can also be quantified through measurement of three fundamental neurophysiological properties: 1) the threshold (the amount of energy required to generate nerve firing); 2) the latency (the amount of time it takes for an electrical signal to propagate between two points of interest in the nervous system); and 3) the amplitude (the size of the response, which reflects the number of nerve cells that have activated). This testing is analogous to Peripheral motor system assessment performed routinely using Electromyography / Nerve Conduction Studies (EMG/NCS). Recent research has shown that Transcranial Magnetic Stimulation (TMS) may be used for this purpose but, unlike EMG/NCS, TMS is not yet FDA Approved for routine motor system diagnostics in the United States (although repetitive TMS is cleared by the FDA for treatment of depression). At Cincinnati Children's Hospital Medical Center (CCHMC), our laboratory has been using TMS for research in children and adults to understand normal motor system development, and abnormal motor function in Attention Deficit Hyperactivity Disorder (ADHD) and Tourette Syndrome (TS) for over 5 years. In this study we propose a preliminary investigation to assess feasibility of use of TMS for diagnostic purposes. Our primary aims are: 1) to use TMS to collect neurophysiologic data in children with motor disorders, 2) to use TMS to generate hypotheses and preliminary findings in motor system diseases which can be used for preliminary data in future scientific studies and grant applications.

Keywords: Neurological disorders, development, motor evoked potentials, Transcranial Magnetic Stimulation

II. PURPOSE OF STUDY

The purpose of this study is to use Transcranial Magnetic Stimulation (TMS) to study diseases that affect the motor system. Motor movements are generated through a complex system of pathways between the cerebral cortex, basal ganglia, thalamus, cerebellum, brainstem, spinal cord, nerve plexus, peripheral nerve and muscle. A disruption anywhere along this system can cause abnormal motor function. Such disruptions cannot always be seen using neuroimaging. We propose to use TMS to collect neurophysiologic data in diseases that affect the motor system in hopes of improving our understanding of and ability to care for children. Utility of TMS for these purposes has recently been reviewed [1] and thus far most studies are in adults.

The clinical applications we propose to investigate, arranged anatomically with selected published references include:

Table 1

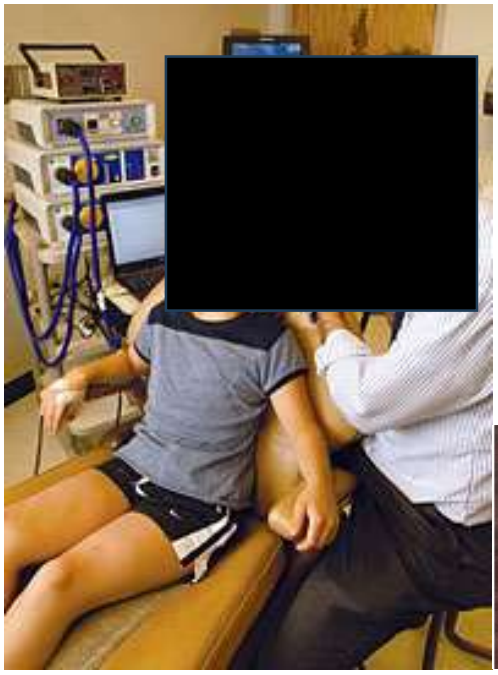
Location in the Nervous System	**Disease, Disorder, or Pathological Process**	**Technique**
Cerebrum [2-5]	Stroke/ischemia, cerebral palsy, neurodegenerative diseases, demyelinating diseases	Single Pulse TMS, Paired Pulse TMS, Theta Burst Stimulation
Basal ganglia [6-11]	Dystonia, chorea, tic, stereotypy, Tourette Syndrome	Single Pulse and Paired Pulse TMS, Theta Burst Stimulation
Cerebellum [12,13]	Congenital cerebellar malformations, Neurodegenerative Diseases and ataxias	Paired pulse cerebellar-cerebral TMS, Theta Burst Stimulation
Spinal Cord [14-16]	Trauma, stroke, demyelinating diseases, transverse myelitis	Single Pulse TMS
Brachial plexus, lumbar plexus [17]	Congenital malformations, birth trauma, ischemia, tumor, avulsions	Single Pulse TMS
Nerve roots, peripheral nerves [18,19]	Guillain-Barre syndrome (AIDP), CIDP	Single Pulse TMS
Anywhere along cortico-spinal pathway [20,21]	Psychogenic paralysis	Single Pulse, Paired Pulse TMS, Theta Burst Stimulation

This protocol is open, to allow exploration of TMS as a clinical tool (similar to NCS/EMG and Somatosensory Evoked Potentials) and hypothesis generating. We propose to study the utility of single and paired pulse TMS for understanding central nervous system pathology in diseases and disorders affecting the motor system. The members of divisions of neurology, neurosurgery, rehabilitation, and orthopedics or other divisions would subsequently be able to use these findings as preliminary data for hypothesis driven research.

III. SIGNIFICANCE OF STUDY IN RELATION TO HUMAN HEALTH

Routine testing of neurophysiology and function of peripheral nerves and muscle is important for patient care in neurological diseases of the peripheral nervous system. Testing in the peripheral nervous system of motor and sensory pathways (NCS) in the arm and hand are shown in Figure 1. Testing in the central nervous system of visual pathways (Visual Evoked Potentials), auditory pathways (Brainstem Auditory Evoked Responses), and sensory pathways (somatosensory evoked potentials) are also standard medical tests. These types of evoked potential studies are in routine clinical use at CCHMC, providing clinically useful information. This protocol extends these principles to the CNS motor system.

Noninvasive assessment of neurophysiological properties of the CNS using TMS with a hand held magnetic coil was described in 1985 [22]. Clinical applications of magnetic stimulation of brain, spinal cord, and nerves have been expanding since that time. Magnetic stimulation of the peripheral nervous system is approved by the FDA. Repetitive TMS was recently cleared by the FDA for use in treatment of depression. We have used a Magstim TMS device in our laboratory for over 5 years with no significant adverse events. In this study, we propose to use TMS to gather neurophysiologic data to characterize different types of diseases and disorders that affect the motor system in children, to improve our diagnostic and therapeutic management. Although this is a study of feasibility and data gathering rather than hypothesis testing, we anticipate some data will be publishable because of the novelty of this emerging technology.



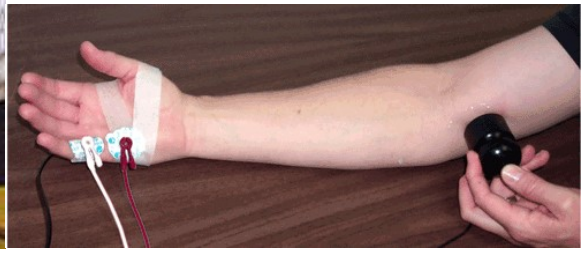


Figure 1. At left, research use of Transcranial Magnetic Stimulation over motor cortex to measure neurophysiology of central nervous system. Below, routine clinical electrical stimulation to measure neurophysiology of peripheral nerves.

We believe that the current protocol, which involves single or paired pulse TMS administered with field strength of 2 Tesla or less, consistent with the field strength of clinical MRI, constitutes a minimal risk use of the TMS devices, with potential for direct benefit in some applications.

CCHMC has a large and diverse group of specialists that treat diseases and disorders of the central nervous system. Clinicians include neurologists, neurosurgeons, orthopedic surgeons, physiatrists, radiologists, psychiatrists, and psychologists. A vast array of imaging technologies provides exquisitely sensitive and anatomically specific information about neurological diseases. Imaging techniques in use at CCHMC include Computed Tomography (CT), Magnetic Resonance Imaging (MRI) (1.5 and 3 Tesla magnets), Functional MRI, Single Photon Emission Computed Tomography (SPECT), and Positron Emission Tomography (PET). Because the nervous system uses electro-chemical signaling, the central nervous system may also be assessed with neurophysiological techniques including electroencephalography (EEG) and magnetoencephalography (MEG). Each of these studies provides useful information, but has some limits in terms of sensitivity, specificity, time, cost, need for sedation, and patient tolerability. TMS may ultimately join these other technologies in providing useful clinical information to a wide variety of specialties.

This possibility can be understood through describing some representative scenarios:

Clinical scenarios

Acute Spinal cord disease - transverse myelitis: child presents with progressive and ultimately complete flaccid paralysis of the legs. MRI imaging shows signal change for 2

cm in the thoracic spinal cord, consistent with a diagnosis of *transverse myelitis*. Clinical question: is there preservation of motor pathways to the legs?
TMS tests: Double cone coil over vertex, round coil over lumbar spine/plexus. Surface EMG over lower leg (anterior tibial) muscle.
Possible results: Lumbar plexus stimulation produces normal responses in the legs. Brain stimulation shows prolonged latency (slow conduction time) from brain to lower spine, with small amplitude motor evoked potential in the leg. This suggests that despite complete loss of movement of the legs and signal change in spinal cord, there are some preserved, intact motor fibers running through the spinal cord. Injury involves both demyelination and axonal damage. (Note - Somatosensory Evoked Potentials are currently used clinically to assess sensory pathways in spinal cord. TMS could complement this by assessing motor pathways. TMS is also much quicker and probably more comfortable.)

Chronic Spinal cord compression due to orthopedic disease: child presents with progressive scoliosis. Clinical question: Is there cord compression affecting motor pathways?
TMS tests: Double cone coil over vertex, round coil over lumbar spine/plexus. Surface EMG over lower leg (anterior tibial) muscle.
Possible results: Monitored over a period of months to years, no change in motor potentials. This supports deferring surgery in the proper clinical setting.

Chronic Spinal cord and brainstem compression - Chiari I*:* Child presents with asymptomatic or minimally symptomatic Chiari I malformation. Clinical question: is there compression of the spinal cord?
TMS tests: Double cone coil over motor cortex. EMG electrodes are placed in either upper or lower extremities.
Possible results: Patients with abnormal central motor conduction time (CMCT) but are still asymptomatic or minimally symptomatic may need to be referred for decompression surgery.

Brachial plexus - neonatal: Child presents with upper brachial plexus (Erb's) palsy at birth. Clinical question: What is the potential for recovery?
TMS tests: Figure 8 coil over motor cortex, round coil over cervical spine/ brachial plexus. Surface EMG will be placed over the bicep muscle.
Possible results: Complete absence of bicep signal. If our experience shows we can usually reliably obtain biceps signal, then the absence of signal of may be an indication of severe damage.

Basal ganglia - Sydenham Chorea: Child presents with SC and is prescribed neuroleptics for symptom control. Clinical question: Can medication be discontinued?
TMS tests: Figure 8 coil over motor cortex. Surface EMG is placed over upper extremity. There are currently minimal neurophysiological data regarding SC.
Possible results: The extent of abnormal neurophysiological data correlates with symptom severity, predicts recovery, aids in treatment decisions.

Cerebellum - tremor: Child presents with unusual intention tremor. Clinical question: Is the tremor dystonic or cerebellar?
TMS tests: Paired pulse cerebellar/motor cortex.
Possible results: Failure to find the normal cerebellar cortical inhibition (interstimulus interval 6 msec). This suggests cerebellar pathology is present and may guide further testing or pharmacological treatment with medications used for essential tremor.

Cerebellum - ataxia: A new therapy is developed for a degenerative ataxia, e.g. for Freidreich's [23]. Investigators wish to monitor the effects with a simple, short clinical test that does not require sedation. Ataxia is challenging to accurately rate. Question: Is cerebellar-cerebral inhibition a biomarker of cerebellar response to treatment?
TMS tests: Paired pulse cerebellar/motor cortex.
Possible results: Drug treatment, but not placebo treatment, is associated with a normalization of neurophysiological measures.

Metabolic or genetic leukodystrophies: A new therapy is developed for a degenerative white matter disease. Clinical rating scales of disability and impairment are insensitive to early effects of treatment. Clinical question: Is central conduction a biomarker of white matter regeneration and repair?
TMS tests: Single pulse TMS in motor cortex; paired pulse cerebellar/motor cortex.
Possible results: Beneficial treatment modifies central conduction velocities, predicting clinical subsequent improvement.

Possible Psychogenic Disorder*:* Patient presents with abnormal movement(s) or paralysis. There is suspicion that the symptoms are psychogenic in origin. Clinical question: Are symptoms psychogenic? I.e. is motor system physiologically intact?
TMS tests: Double cone coil over motor cortex. Electrodes are place over limb.
Possible results: In psychogenic conditions, neurophysiologic results should be normal. This may save time and resources as it may eliminate the need for other costly or risky diagnostic tests.

IV. PREVIOUS WORK DONE IN THIS AREA

Transcranial Magnetic Stimulation (TMS) has been used in humans, in essentially its current form, for 20 years [22]. Several companies make TMS devices. Each involves a pulse generator which stores electrical energy (from a wall outlet) connected to a hand-sized coil, usually round or figure-of-eight shaped. The operator or a computer can trigger the generator to release electricity into the coil which produces a transient magnetic field beneath the coil. When the field change occurs near neurons, they may depolarize (fire), producing a measurable response. The maximum field strength for the Magstim TMS device which we have used at CCHMC is 2 Tesla (comparable to 1.5 and 3 Tesla magnets used for clinical MRI scans).

The Magstim TMS BISTIM (used at CCHMC since 2001) and Rapid2 Stimulators (used at CCHMC since 2008) are approved in the United States for peripheral nervous system stimulation, but not for routine clinical diagnostic or therapeutic central nervous system

applications at this time. Many neurophysiology laboratories, including ours, have used TMS as a non-invasive technique to measure neurophysiological properties of the central nervous system in children. TMS is ideal for studying the motor system, but has other applications as well. It is well tolerated by most children, with minimal or no discomfort. In our prior IRB-approved studies, we have used series TMS to study motor cortex physiology in healthy children as well as children with Tourette Syndrome and Attention Deficit Hyperactivity Disorder (ADHD).

V. PRELIMINARY DATA IN CHILDREN

For the scenarios above and described in Table 1, we do not have preliminary data. This study is exploratory. However, we are currently using TMS as part of an NIMH-funded study to understand motor development in typical and ADHD children (CCHMC 06 10 35). In this ongoing study of ADHD vs. typical children between the ages of 8 and 12 years, we do have some data that might be useful for comparison. For example, motor threshold correlates highly with age: $r = -.63$, $p < .001$; $n = 72$ children (preliminary analysis, data unpublished, study ongoing). The mean threshold is 68% of maximal stimulator output, and the Standard Deviation is 16%.

VI. RESEARCH PLAN

1. ***Number of subjects and methods of selection*****:**

i. For this study, we are requesting permission to recruit up to 300 children and adults at CCHMC.
ii. Study eligibility will be determined by the principal investigators Dr. Gilbert or Dr. Wu in consultation with the managing physician, based on presence of motor system problems described in Table 1.

2. ***Inclusion and Exclusion criteria*****:**

Inclusion Criteria

i. Either gender, any race, ethnicity or socioeconomic status
ii. Children greater than 2 years old and adults less than 60-years old with diseases affecting the motor system and interfering with voluntary movement. Adult diseases would typically have childhood onset, e.g. spinocerebellar ataxia, degenerative leukodystrophies, spinal cord disease.
iii. Healthy individuals recruited for comparative normative data.

Exclusion Criteria

i. Standard contraindications to TMS: Implanted brain stimulator, vagal nerve stimulator, VP shunt, aneurysm clip, cardiac pacemaker, or implanted medication port.
ii. Other situations where it is reasonable to avoid TMS: Pregnant females or sexually active females not using birth control. Significant medical conditions including kidney disease, anemia, thyroid disease, lung disease, heart disease. In

addition, any conditions, in the judgment of the investigators, for which external magnetic stimulation might risk harm.

3. *Randomization*:
NA

4. Study Procedures:
Prior to participation, parents will sign consent forms and children older than 11 years will sign assent forms.

Participation in this study and use of TMS will not in any way influence standard medical care, in order to minimize coercion.

Diagnostic information obtained through this study is not part of standard medical care and will not be available to clinicians.

This study has 4 parts, listed here and described in greater detail below:

1. Collection of routine clinical data obtained during standard of care evaluations in children with neurological conditions.
2. Administration of TMS as described in Table 1 and in the clinical scenarios above.
3. Data storage, analysis, comparison with prior CCHMC and published data.
4. Use of data for hypothesis generation, effect and sample size calculations for future studies.

Routine Clinical Data Acquisition
Clinical and demographic information will be obtained after informed consent. This information will include diagnosis, results of imaging, laboratory, or neurophysiological studies as appropriate. When appropriate, the following clinical rating scales may be used – Yale Global Tic Severity Scale [24], Premonitory Urge Rating Scale [25], Children's Yale-Brown Obsessive Compulsive Scale [26] and DuPaul ADHD Rating Scale [27].

TMS – details:
TMS will be performed using a Magstim 200® stimulator (Magstim Co., New York, NY, USA) connected through a Bistim® module to a TMS coil as described in CHMC 06-10-11; 05-05-19; 03-05-52; 03-05-53. A 70 mm double cone coil will be used for lower limb stimulation – see below. Currently the lab has 90 mm circular, 70 mm figure-8 and 40 mm figure 8 coils.

The subject sits in a comfortable dental chair or lies prone on a hospital bed. The TMS devices are maintained in the EEG suite, which is under direct supervision of laboratory personnel during business hours and is locked with restricted key access during all other hours.

Motor cortex stimulation for upper limb: The TMScoil is placed with its center near the vertex in the optimal position and orientation for producing a motor evoked potential (MEP) in the bicep, tricep, abductor pollicis brevis (APB) muscle, first digital inter-osseous (FDI) muscle, or abductor digiti minimi (ADM) muscle, as the clinical context requires.

Motor cortex stimulation for lower limb: The motor cortex that controls leg and foot lies along the inter-hemispheric frontal lobe and can be better stimulated using the double cone coil over the vertex.

Cerebellar stimulation The cerebellum will be stimulated 1-2 cm lateral and caudal (below) the inion (the protuberance at the back of the head) as described by Ugawa and colleagues.[12]

Plexus stimulation The spinal cord will be stimulated with the patient prone and the figure 8 or round coil placed at the level of the cervical/brachial plexus or lumbar spine/plexus.

Priming cortex for children with high thresholds Some young children and all infants have high thresholds for stimulation. The low intensity, intermittent Theta Burst Stimulation (iTBS) potentiation protocol used in IRB approved protocols CHMC 2008-1237 and 2008-1256 will be used as needed to facilitate single and paired pulse TMS measures.

Repetitive Stimulation Repetitive stimulation of the cortex will be performed using Theta Burst Stimulation (TBS). TBS protocols are currently used in IRB approved protocol CHMC 2008-1256. The use of these protocols is well documented in the medical literature [28-31]. For the CHMC 2008-1256 study, we have already performed TBS on 63 pediatric/adult subjects and all the subjects have tolerated the protocols well without serious adverse events.

Functional TMS Single and paired pulse TMS, as above, performed dominant or non-dominant motor cortex during bimanual tasks, response inhibition tasks, and reward paradigms. Functional TMS will also target cortical regions that are important for motor control and motor response inhibition. These regions will include supplementary motor complex and inferior frontal gyrus.

Goniometer The investigators will quantify motor movements of the hand using a goniometer. The device was used in a prior IRB-approved study (#2008 – 0061) [32]. The device quantifies finger movements through a soft, bendable plastic transducer. The transducers are attached to the fingers by a Velcro (see figure to the right). This device is strictly used to detect finger movements and does not involve delivering any energy (i.e. electrical current) to the hand; therefore, the addition does not change the adverse risk profile of the study. Part of the goniometer procedure requires videotaping of hand movements.

Electroencephalography (EEG) EEG will be used to assess the electrophysiologic correlates of movements and/or TMS. EEG will be recorded with whole dense array electrode caps using continuous recording EEG system (Electrical Geodesics, Inc. (EGI), Eugene, OR, USA) or BrainVision actiCHamp EEG system (Brain Vision LLC, Morrisville NC). Dense array electrode caps include 32, 128 or 256-channel electrodes. The sensor net uses a mild, fragrance-free, saline-based solution or gel to contact the scalp, requires approximately 10 minutes to position the net and does not require abrasion of the skin as the EGI amplifiers are design to tolerate normal skin impedances. This system of electrodes and amplifiers can be left in place during TMS stimulation.

The position of the EGI electrodes are captured with the Geodesic Photogrammetry System (GPS), which is a precision geodesic dome of 11 cameras that quickly simultaneous photograph the net on the subject's head. The time of the photographing is just the time required to seat the subject in the chair and take the photograph. The precise 3D location of the sensors is digitized offline afterwards with software supplied with the system.

Brain MRI

Brain MRI may be performed to help with neuronavigation for TMS. This will be done in the Imaging Research Center 3.0 Tesla MRI scanner. A registered radiological technologist will explain the procedure and review the standard checklist of patient questions used for MRI protocols. In preparation for the scan the participant will first be asked to remove all jewelry, pens, pencils, credit cards, belt buckles and any other metallic objects from clothing. The participant will be given a pair of disposable foam ear plugs and instructed on how to insert them for optimal ear protection. The technologist will ensure that the earplugs are inserted prior to scanning. Fiducial markers will also be placed in three different locations on the face for facial landmarks . Easily-removeable and disposable fiducial markers are small, soft, circular stick-ons that are placed in the area of interest during imaging as reference points. In the case of this study, three will be placed around the face that will show up clearly on the images post-scan to guide neuronavigation during TMS. Since 2009, neuronavigation in the lab has been conducted using BrainSight® (Rogue Research, Montreal, Canada). Current version is 2.3.12 but will be updated in the future per manufacturer recommendations.

All brain MRI images will be reviewed by a pediatric neuroradiologist. If any clinically significant findings is present, the PI will discuss with the family. In such case, if the subject or guardian consents, the PI may discuss these findings with primary care physician and ensure that appropriate referral is made. Neither sedation nor contrast will be used in the brain MRI.

Behavioral Tasks Various behavioral task(s) may be performed to assess the effects on motor control.

Eye Movements Participants will be monitored or asked to make specific eye/eyelid movements. A false belief behavioral task may be used in conjunction to monitor eye movements [33]. This task involves the subject to look at a sequence of an actor and a puppet moving a ball between two boxes. The resulting ocular movements will be recorded using a Tobii Eye Tracker (Tobii Technology AB, Danderyd Sweden).

Probabilistic Learning Probabilistic classification learning is a task that requires activation of the frontostriatal network, which modulates motor preparation and movements. The task performance has been shown to be abnormal in several movement disorders – Parkinson's disease, Tourette Syndrome, Huntington Disease [34-36]. This task involves the subject to predict a binary outcome (positive or negative) based on looking at a sequence of four items (i.e. cards).

Bimanual Tasks In each experiment, the child has both hands relaxed on his lap, on a pillow supporting at the elbows. For the single finger tapping motor task, the child is instructed to repeatedly tap the task hand index finger while keeping the non-task hand in the same position, but relaxed. To ensure consistency in performance speed and coordination, the a computer instructions will be shown to indicate resting, tapping one finger, tapping all fingers sequentially, and sustaining a squeezing of the index finger to the thumb. TMS will be administered as above but during the task.

Response Inhibition Tasks In each experiment, the child keeps both hands relaxed, but on a cue from the computer has to push an X button with the right hand or O button with the left hand, on a game controller. On some trials, a "stop" auditory tone will occur. At time = 0ms, an image of either an X or O will be displayed on the screen. TMS will be administered as above but during the task. Slater-Hammel procedure, another response-inhibition task, may also be used to assess motor response time [37]. This task requires the subject to hold a button and release before a moving marker reaches a predefined time point (800 milliseconds after the start signal). If the marker stops in its trajectory, the participant is instructed to not let go of the button. Another method of comparing response inhibition is to present conditions of just staring at computer screen vs. instructing subjects to activate or inhibit motor movement.

Reward Paradigm In each experiment, the participant watches while smiling or frowning faces appear on the computer screen. Three smiles will result in the participant receiving a monetary award ($0.25). TMS will be administered as above, but during the task.

Money Bags Paradigm In each experiment, the participant clicks the mouse control each time a quarter appears above the money bag on a computer screen. If they click accurately, the quarter drops into the money bag and ($0.25) is registered as gained by the participant. The difficulty and perceived degree of difficulty varies. TMS will be administered during the task.

Selective Suppression via Real Time Feedback In each experiment, the participant receives an instruction to think about moving or not moving either their index finger or their pinky. TMS is then administered and the participant receives immediate feedback on computer monitor about the size of the motor evoked potential (MEP).

EMG recording and signal processing The EMG is recorded with surface electrodes taped to the skin. This is comfortable for the patient as no needle is required to be inserted in the muscle. The signal is amplified, and filtered (100/1000 Hz) (Coulbourn Instruments, Allentown, PA) before being digitized at 2 kHz and stored for analysis using Signal® software and a Micro1401 interface (Cambridge Electronic Design, Cambridge, UK).

Neurophysiological parameters Thresholds defined using conventional criteria as the lowest stimulator intensity that produces measurable responses in 3 of 6 trials. Short intracortical inhibition (SICI) and facilitation (ICF) are measured with a paired-pulse paradigm using three conditions: single pulse, paired pulse at 3 msec interstimulus intervals, paired pulse at 10 msec interstimulus intervals. Subthreshold pulse precedes suprathreshold pulse for paired pulses. Peripheral conditioning pulses are administered 20-30 msec prior to motor cortex. Short ICF will be also performed with a paired-pulse paradigm [38-40]. Long intracortical inhibition (LICI) involves using 100-200 msec interstimulus intervals. In other forms of paired-pulse stimulation such as cerebellar conditioning, pulses are administered 5-10 msec prior to motor cortex. Twenty trials are performed for each ISI and for the test stimulus alone. The order of the intervals is varied randomly, and the interval between trials varies randomly by <10% around a mean of 6 seconds. Transcortical inhibition to the left dominant hemisphere/ right dominant hand is measured by stimulating over right motor cortex, while the child simultaneously contracts muscles in both hands. This produces an evoked potential in this ipsilateral and contralateral hand, followed by periods of EMG silence (the "silent period"). Latency and duration of this silent period are affected both by age and by ADHD diagnosis [41]. Latencies are measured by subtracting MEP onset time from TMS artifact time. Amplitudes are measured as peak to peak and area under the curve.

***5. Questionnaires*:**
NA

***6. Blood Specimens*:**
NA

***7. Previous research studies in which the projected patient population may be involved*:**
There are no issues related to cumulative risk. Participation in several different TMS protocols is allowed but no individual would participate in 2 or more protocols the same day.

8. ***Data Analysis and Sample Size Calculations*****:**

Sample size- general issues
We are requesting permission to enroll up to 300 children and adults. We wish to offer TMS as a potential clinically useful tool and for hypothesis generation in a variety of motor disorders. Statistical analyses otherwise are not planned.

a. The utility of TMS in motor disorders
In adults, the sensitivity of TMS for spinal cord disease has been published as 100% and specificity 85% [16]. Similarly, in adults loss of and preservation of motor potentials are highly predictive of poor vs. good long term outcomes after stroke [5].

b. Quantitative biological markers of motor system disease, assessed using TMS. We anticipate that TMS measurements listed in Table 1 will yield quantitatively abnormal responses, compared to the same measures in healthy children. However, this is a preliminary study, not a formal case-control study. Some of these data, such as complete absence of a response localizing to spinal cord or cerebrum, will be unambiguous. Other measures, similar to some neuroimaging results, may be interpretable in a clinical context. Finally, some measures may ultimately be useful for understanding disease, based on disease vs. control between group differences, in future studies.

c. Reliability and Consistency of TMS Data in our Lab.
Certain measures, such as central motor conduction times, have normative data published. We can use available data as a reference for the data we generate through use of TMS to determine whether data in our laboratory are broadly consistent with those published, but formal statistical analysis is not planned for this aim at this time. In addition, although we do not have funding at this time for generating normative and disease related pediatric datasets and test-retest datasets, we plan to store our data and thereby have some ability to assess this. We have previously published test-retest data in Tourette Syndrome and ADHD for a measure of motor cortex inhibition [42].

9. ***Facilities*****:**
Studies will be performed in the Division of Neurology and Neurophysiology/TMS /MEG/EEG Laboratory at Cincinnati Children's Hospital Medical Center.

VII. SPECIAL CONSIDERATIONS

1. Radiation Safety: NA
2. Investigational Devices: The TMS apparatus is investigational, although it has recently been cleared for treatment of refractory depression. We consider 2 Tesla or less stimulation or brain, cerebellum, spinal cord, and nerves to be a non-significant risk use of the TMS device. Manufacturer's information for the

Magstim device has previously been submitted to the IRB and is available on request.

3. IND (Investigational New Drug): NA
4. Emergency Use: NA
5. CCHMC Pharmacy: NA.
6. Discarded Tissues: NA
7. Tissue Banks: NA
8. Genetic Studies: NA
9. Institutional Biohazard Committee: NA
10. Imaging: NA

VIII. POTENTIAL BENEFITS

There is a potential for direct benefit by participating in this study if the clinical neurophysiological information is useful to the managing physician.

IX. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES, AND PRECAUTIONS

1. Known and potential discomforts or hazards of single and paired pulse TMS:
Single and paired pulse TMS has been used at CCHMC under Dr. Gilbert's direction since 2001 for research only. Potential discomforts are mild and transient. In a prior study of 40 healthy and ADHD children, Garvey et al asked children to rank TMS compared to other childhood activities. TMS was ranked preferable to 1) a "shot"; 2) going to the dentist; and 3) a long car ride [43]. The following mild, transient effects were reported in our prior study of 35 children and adults: scalp discomfort (12%), hand weakness (9%), headache, neck pain, arm pain, and arm tingling (6%), hand pain, decreased hand dexterity, hearing changes, and tiredness (3%). All of these had resolved by the following day. There were no physical findings after TMS supporting the subjective descriptions of loss of strength or dexterity. Furthermore, a consensus statement from the international TMS community concluded that "single-pulse and paired-pulse TMS in pediatrics is safe for children two years and older."[44] A prior common concern about use of TMS was the risk of seizures[45]. We follow recommended guidelines [45] and have seen no seizures in children or adults studied at our center. In addition, more recent studies even in children with epilepsy suggest that the risk of TMS inducing seizures is quite low.

2. Precautions, risk minimization:
The protocols include a number of precautions to minimize risk. The TMS laboratory was established in 2001 in consultation with Dr. Eric Wassermann, an internationally known researcher in transcranial magnetic stimulation. Dr. Gilbert or Dr. Wu will be present during TMS. All subjects will wear 34 NRR earplugs or headphones during TMS if the head is stimulated at an intensity of over 90%. Standard exclusion criteria are applied for participation in this study. Detailed questioning for any adverse events will occur after the experiment and the next day after the study.

3. The method of monitoring study conduct.

Adverse events will be reviewed using direct questions with a detailed review of systems on the day of the study and by phone the next day. The principal investigator is responsible for reporting adverse events to Cincinnati Children's Hospital Medical Center Institutional Review Board.

4. Methods for maintaining data quality and confidentiality:
Data are maintained in case report folders identified only by an anonymous subject ID, in the locked principal investigator's office which is situated in a locked office suite. All data kept in computerized files are in computers or a server with restricted, password-protected access.

5. An assessment of accrual (timely enrollment) and the handling of dropouts.
Accrual rates will be monitored by the principal investigator.

7. Data Safety Monitoring Plan:
The data safety monitoring plan is to review adverse events at weekly meetings of the TMS research group.

X. PROPOSED RISK BENEFIT ANALYSIS
In the opinion of the investigative team, this study, based on our experience administering TMS as well as the published literature on TMS, involves minimal risk, with potential for direct benefit.

XI. SECURITY/CONFIDENTIALITY
Privacy of the individuals participating in this proposed study will be maintained through non-identifying subject ID codes, locked storage and password protected files. The study log will be maintained in a password protected folder on the desktop computer of the principal investigator. Case reports and spreadsheets will refer to subjects by number only. Subjects will be informed that, if necessary, the IRB or FDA may review the data.

XII. DURATION
We estimate the proposed study to take 6 years to complete.

XIII. FUNDING
Movement Disorders Research Fund.
Tourette Association of America until 4/30/2020.

XIV. PAYMENT FOR STUDIES
There will be no charges to patients or to third party payers related to participation in this study. Subjects will be paid $15/hour (prorated) for completing this study.

Payment will be in the form of a reloadable debit card (ClinCard). We will provide the card and load money onto the card after each completed visit based on the schedule listed above. We will also administer a handout that will explain how to use it.
Because this research study involves payment for participation, we are required by federal Internal Revenue Service (IRS) rules to collect and use participants' social

security or tax ID number (SSN) in order to track the amount of money that we pay. Unless we have been given specific permission for another use of participants' SSN related to this research, we will only use the participants' SSN to keep track of how much money we pay to them and their SSN will not be used as part of this research.

XV. RECRUITMENT

Potential participants will come from several sources:

Clinically affected subjects will be recruited from the neurology inpatient service, the neurology consult service, and subspecialty clinics in neurology, neurosurgery, orthopedics, rehabilitation medicine, developmental and behavioral pediatrics, and psychiatry. For many physicians in these subspecialties, basic neurophysiological principals are already understood because these physicians use peripheral nerve Electromyography (EMG)/Nerve Conduction Studies (NCS) in patient care. We will inform relevant subspecialties at faculty meetings or through individual, in-person meetings. Persons interested in referring a patient for TMS will call or email the study staff and there will be physician to physician discussion of the neurological condition. Healthy persons will be recruited via advertisement.

Before any study measures are performed, the patient's physician, or the study physicians, will explain to the subject/parent that TMS is cleared by the FDA for treating refractory depression but is not approved for diagnosis of conditions affecting the motor system. The patient will be told that the TMS measures will only be used for research purposes. The children/parents will be given an informed assent/consent form to read. This will include a number at which the subject/parent may reach the study physicians, in the case that they have any questions. After all questions are answered and assent/consent signed, the study can proceed.

Individuals have the option to choose not to participate in the study without revealing the reason. Participation or non-participation will not affect the provision of health-care to the subject in any way.

XVI. PERMISSION OF PATIENT'S ATTENDING PHYSICIAN

Managing physicians interested in these TMS procedures will directly contact members of the TMS study team, so they will be aware of the study.

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