Protocol

Title: Changes in Cortical Oscillations Induced by rTMS Therapy in Patient Populations with Tremor

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Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal movements and/or postures [1]. In some patients, they experience both the dystonic symptoms and also an oscillating tremor and these patients are referred to as having dystonic tremor (DT). Here, the contractions are intermittent and oscillatory, and movement can appear rhythmical. When DT appears in the arms, it is similar to symptoms of another movement disorder called essential tremor (ET). Sometimes, DT and ET can be misdiagnosed. These disorders are associated with a loss of inhibition along different levels of the central nervous system. Non-invasive modalities of brain stimulation that can modulate cortical excitability, such as repetitive Transcranial Magnetic Stimulation (rTMS), have been proposed as an alternative therapeutic opportunity to correct the loss of inhibition. However, studies analyzing the effects of rTMS on dystonia populations have shown contradictory results [2], ranging from mild to non-detectable clinical benefit over short periods of time. Many of these studies use clinical scales as the only outcome measure, which may not be sensitive enough to capture minor changes in cortical activity. These inconclusive findings have complicated what future directions to take with this approach. Therefore, there is merit in assessing whether any therapeutic change is occurring in the cerebral cortex using more sensitive measures of the physiology.
In prior work [3][4], we have used high-density electroencephalography (EEG) to study DT and ET. We have found that in both groups, patients exhibit attenuated changes in alpha (7-12 Hz) and beta (12-30 Hz) band activity over the motor cortices during a force control task. Irregular activation of the motor cortices has also been confirmed in fMRI studies [5]. We propose using EEG as an outcome measure to detect changes in cortical oscillations caused by rTMS in patient populations with tremor. The near millisecond resolution of EEG will allow us to detect changes in distinct frequency bands in signals recorded from the cortex.

The **primary goal** of this study is to compare differences in cortical activity of patients with dystonia and/or tremor before and after applying a session of rTMS. Specifically, we will apply rTMS to the primary motor cortex (M1) as our group and others have shown abnormal function of the region. Moreover, a study [6] shows that targeting of M1 and the dorsal premotor cortex (dPMC) with rTMS results in a trend towards improved clinical outcome in patients with focal hand dystonia and cervical dystonia.

The **central hypothesis** of this study is that rTMS can modify cortical oscillations in patient populations with dystonia and/or tremor and that we will be able to detect these changes with the use of EEG. By applying inhibitory rTMS to the motor cortices, we may expect a shift in cortical oscillations towards normal activity.

Specific Aim 1: Determine therapeutic effect of rTMS on the cortex of patients with Dystonia

We will determine any therapeutic effect of a 1-Hz rTMS session on the primary motor cortex of patients with dystonia by comparing the differences in cortical activity of healthy controls and patients with dystonia pre-rTMS session to the differences in cortical activity of healthy controls and patients with dystonia post-rTMS session. We hypothesize that after the rTMS session, the cortical activity of patients with dystonia will shift towards the cortical activity of healthy controls.

Specific Aim 2: Determine therapeutic effect of rTMS on the cortex of patients with tremor

We will determine any therapeutic effect of a 1-Hz rTMS session on the primary motor cortex of patients with tremor by comparing the differences in cortical activity of healthy controls and patients with tremor pre-rTMS session to the differences in cortical activity of healthy controls and patients with tremor post-rTMS session. We hypothesize that after the rTMS session, the cortical activity of patients with tremor will shift towards the cortical activity of healthy controls.

Study Design: Subjects diagnosed with Dystonia and/or tremor will be enrolled. Diagnosis of Dystonia and tremor will be established in accordance with the Consensus Statement of the Movement Disorders Society [1]. In this study, we plan to recruit up to **60 subjects with Dystonia and/or tremor** in the age range of 21-80 years. Specifically, our inclusion criterion is: Diagnosis of Dystonia and/or tremor according to the Consensus Statement of the Movement Disorders Society. We will exclude patients with 1) pregnancy; 2) active seizure disorder; 3) presence of a metallic object such as a pacemaker, implants, metal rods, and hearing aid, 4) history of stroke. We will also identify subjects who meet inclusion/exclusion criteria from the IRB approved INFORM database (IRB#201501166). These subjects have consented to being contacted for future research. We will enroll up to **30 healthy controls** of similar age distribution and sex ratio as the Dystonia and/or tremor group for normative electrophysiological data. Controls will be recruited through fliers placed across campus. Additionally, we will use databases to identify healthy controls that are willing to be contacted through Health Street and Consent2Share. Controls must be free from a diagnosed neurological disorder. We will exclude controls with 1) pregnancy; 2) active seizure disorder; 3) presence of a metallic object in their brain, 4) any history of stroke.

Electroencephalography (EEG) will be used as the primary outcome measure. Repetitive Transcranial Magnetic Stimulation (rTMS) will be used over the motor cortices as an intervention that is expected to have short-term (less than an hour)

electrophysiological effects. EEG will be collected before and after administration of rTMS. A waiting period will follow to allow the short-term effects of the intervention to subside, after which a third EEG procedure will be repeated.

In a subgroup of participants with a mild to moderate severity tremor (n = 20), we will use rTMS over the cerebellar cortex and motor cortex on two separate days to collect EEG before and after for assessment of electrophysiological effects. The subgroup will also receive testing and treatment in addition to what is proposed for the primary group. However, the subgroup will complete stimulation delivered to the motor cortex and to the cerebellum on two separate days. The rTMS parameters will be same for motor cortex and cerebellum. The participants who meet the severity tremor criteria and agree to participant in the subgroup will be scheduled on two testing days at least one week apart to allow adequate wash-out time. For the second visit, we may not repeat clinical assessments if the results from the first assessment are deemed sufficient.

Eligible subjects will be invited to the Laboratory for Rehabilitation Neuroscience. We will obtain IRB approved informed consent. Subjects will be explained in detail about the procedures outlined for the study. In order to characterize the current clinical progression of disease we will administer a subset of the following assessments: Montreal Cognitive Assessment (MoCA), Beck Depression Inventory (DBI), Ambulatory Parkinson's Disease Monitoring (APDM), The Essential Tremor Rating Assessment Scale (TETRAS), and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Once completed, subjects will be fitted with an EEG cap and have the electrode holes of the cap filled with conductive gel. The electrodes will be placed and then resting-state EEG and/or task-based EEG will be collected. Resting-state EEG will have subjects sit down and rest, without falling asleep, for no longer than 20 minutes. Task-based EEG will have subjects perform a pinch grip task lasting no longer than 30 minutes. For the pinch grip task, subjects will be signaled to produce a pre-determined amount of force on loadcells using one hand. They will be provided with visual feedback on a screen so that they may see how much force they are producing relative to the target force. Once the EEG procedure is conducted, the rTMS intervention will be administered to the targeted region for only the patient groups. Afterwards, the same EEG procedure conducted before the rTMS will be performed to capture the effects of the intervention. Once completed, the waiting period will occur. Once the period ends, the EEG procedure will occur again. Controls will perform all tasks except for the rTMS intervention.

Outcome measures: The primary outcome measure will be EEG cortical recordings. EEG is an electrophysiological imaging method used to record electrical activity of the brain. It is non-invasive and provides information about the behavior of neuronal populations below the scalp. This is useful to our study because we expect rTMS to alter the excitability of neurons in the motor cortex. We will also collect electromyography (EMG) data from hand and neck muscles as a secondary measure.

Clinical assessments: We will use certain clinical assessments to characterize the mental state, mental ability and motor symptoms of subjects enrolled in this study.

(1) The Montreal Cognitive Assessment (MoCA) is a widely used screening tool for detecting cognitive impairment and mild cognitive impairment.

(2) The Beck Depression Inventory (DBI) is a widely used psychometric test for measuring the severity of depression. It consists of 21 multiple-choice self-reporting items.

(3) The Ambulatory Parkinson's Disease Monitoring (APDM) is used to assess sway, balance and gait. This device uses six wearable sensors to assess kinematics of the body during everyday movement tasks.

(4) The Essential Tremor Rating Assessment Scale (TETRAS) is used to quantify essential tremor severity and its impact on activities of daily living. This rating scale will be video recorded with the participant's permission to ensure reliability of ratings.

(5) The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is used to quantify the severity, disability and pain associated with cervical dystonia. This rating scale will be video recorded with the participant's permission to ensure reliability of ratings.

Not all of these assessments will be performed as they may not be relevant to certain groups. For example, assessment (4) and (5) are only relevant to patients with essential tremor and cervical dystonia.

rTMS therapy

Stimulation: rTMS will be delivered over a single M1 hemisphere, using a Magstim Rapid^2 TMS therapy system (Magstim Inc., Eden Prairie, MN, USA) [7]. The coil that delivers the magnetic pulses will be placed over the hand region of M1, which can be found near the C3/C4 locations of a 10/20 electrode system [8]. The coil position will be marked on the EEG cap with a small circular sticker. 1800 pulses will be delivered in 3 separate trains of 600 pulses at a 1 Hz frequency and at an intensity of 90% of the resting motor threshold (RMT). A 1-minute break will occur between trains for a total duration of 32 minutes. This stimulation protocol is adapted from a previous study [9]. The RMT will be defined as the lowest stimulation intensity required to evoke a 50 μV potential in a target muscle recorded using electromyography (i.e. first dorsal interosseus muscle in our case). During rTMS, all patients will wear ear plugs in order to protect the ears from the acoustic artefact associated with the discharge of the stimulation coil.

Safety of rTMS: Repetitive TMS can have undesired side effects [10]. The proposed study will use TMS parameters well within the published safety guidelines adopted by the International Federation for Clinical Neurophysiology and subsequently updated [11][12]. We will conduct careful monitoring of the participants and follow all recommended precautions for the application of TMS.

For the subgroup (n=20), we will use a low frequency (1 Hz) stimulation dose. Stimulation at this frequency has not been associated with adverse effects. Table 1 (S. Rossi et al., 2009, p. 2016) of the safety guidelines article covers the safety aspects. Our study also involves 1800 pulses at 1 Hz frequency (32 minutes long) delivered over

two sessions about one week apart, which is a much lower dose compared to FDA approval of daily session of 3000 pulses at 10 Hz frequency (45 min daily) for 30 consecutive sessions for medication refractory depression.

Table 1
Potential side effects of TMS. Consensus has been reached for this table.

Side effect	Single-pulse TMS	Paired-pulse TMS	Low frequency rTMS	High frequency rTMS	Theta burst
Seizure induction	Rare	Not reported	Rare (usually epileptic patients; less than 1% in normals)	Possible (1.4% crude risk estimate protective effect) in	Possible (one seizure in a normal subject during cTBS) (see para 3.3.3)
Transient acute hypomania induction	No	No	Rare	Possible following left prefrontal stimulation	Not reported
Syncope	Possible as epiphenomenon (i.e., not related to direct brain effect)				Possible
Transient headache, local pain, neck pain, toothache, paresthesia	Possible	Likely possible, but not reported/ addressed	Frequent (see para. 3.3)	Frequent (see para. 3.3)	Possible
Transient hearing changes	Possible	Likely possible, but reported	Possible not	Possible	Not reported
Transient cognitive/ neuropsychologial changes	Not reported	No reported	Overall negligible (see Section 4.6)	Overall negligible (see Section 4.6)	Transient impairment of working memory
Burns from scalp electrodes	No	No	Not reported	Occasionally reported	Not reported, but likely possible
Induced currents in electrical circuits	Theoretically possible, but described malfunction only if TMS is delivered in close proximity with the elec brain stimulators, pumps, intracardiac lines, cochlear implants)				tric device (pace-makers,
Structural brain changes	Not reported	Nor reported	Inconsistent	Inconsistent	Not reported
Histotoxicity	No	No	Inconsistent	Inconsistent	Not reported
Other biological transient effects	Not reported	Not reported	Not reported	Transient hormone (TSH), and blood lactate levels changes	Not reported

Reimbursement:

Participants will receive $80.00 for taking part in a one-day visit to the laboratory. Participants who are eligible and choose to participate in the two-day visit subgroup study will receive $80.00 for each visit. In addition, they will be reimbursed for travel costs (such as flights, hotels, and/or reimbursement for gas) if they live a minimum of 50 miles away from Gainesville. Finally, during long testing sessions, food and beverages for the participant and any family members and/or caregivers that accompany them to the visit will be provided at no expense to them.

Data Safety Monitoring Plan

The research team monitors the patient safety and data collection of each study visit. The Data Safety and Monitoring Committee will meet once each year to review the recruitment, adverse events, data collection, and other aspects of the study. The Data Safety and Monitoring Committee will be notified of any adverse events that occur during the course of the study, within 2 business days of the specific adverse event. This will allow the DSMC to review any issues that arise in a timely manner. Breaches of

confidentiality will also be monitored by the DSMC. If there is possible harm to subject safety or the possibility of, any harm due to something new that was learned during the study, the DSMC will be convened. Christopher Hess, M.D., Aparna Wagle Shukla, M.D., and David Vaillancourt, Ph.D. will monitor the safety of the project yearly. Dr. Hess will serve as an independent health professional on the Data Safety Monitoring Committee.

Regulatory Approval and Statistics

The study will be approved by the University of Florida Institutional Review Board, and all subjects will provide informed consent. The study is highly feasible given the relatively large number of patients with dystonia and patients with tremor seen at UF and the considerable expertise.

Statistical analysis will be done with R, a free software environment for statistical computing and graphics, and Matlab toolboxes (EEGLAB, among others). For the resting state data, we will use a mixed model ANOVA on the average power of different frequency bands. There will be 2 factors: group (Controls, and tremor groups) and time (3 levels: T0, T1, and T2), where T0 is data collected before rTMS, T1 is data collected after rTMS, and T2 is data collected after the waiting period. For task-based data, we will use EEGLAB to preprocess the data and compute Event Related Spectral Perturbations (ERSPs), a time-spectral graph. From the ERSPs we will run comparisons at each time-frequency point. Because of the large quantity of time-frequency points, we will correct for multiple comparisons.

From previous work [3] we have data about the mean and standard deviation of the average power of the beta band (12-30 Hz) of activity in the brain of ET patients during a force control task similar to the one proposed for this study. We expect to have 3 groups (controls, dystonia and tremor) each built of approximately 30 people. We conducted a power analysis comparing ET vs. control using an independent samples t-test (alpha = 0.05; two-tailed). With this data we predict a 95% power estimate.

	ET		Controls		Power Estimate
	Mean	SD	Mean	SD	
Average beta band (12-30 Hz) power	-2.24	1.57	-3.57	1.24	94.7%

Possible Discomforts and Risks:

There are some possible discomforts and risks for participants taking part in this study.

TMS:

- Headaches – Headaches and neck aches can occur. They can be related to stabilizing the neck when measuring TMS. They are usually short lasting and respond easily to over the counter analgesics.

- Transient hearing threshold shift – There is a possibility of temporary mild hearing loss due to the noise of the TMS machine. The rate of this risk is unknown yet. Earplugs will be provided to the participant to reduce the potential for this risk.
- Seizure – A theoretical risk associated with brain stimulation. In clinical trials using the NeuroStar TMS Therapy® System, which included over 10,000 TMS treatments, no seizures were reported. Since FDA clearance of the NeuroStar Therapy System, the seizure risk is ≤0.1% per patient (less than 1 in 1000 patients). In the event that the participant has a seizure, the study staff will immediately stop the treatment session and make sure that the participant is safe during the seizure. The participant will be watched for a period of time after the seizure to make sure he or she is feeling well. Individuals with an active seizure disorder are excluded.
- Fainting – Not directly related to magnetic stimulation. It is thought to be related to anxiety and psycho-physical discomfort during the procedure. The laboratory is equipped, and staff is trained to respond to this risk if fainting occurs. However, the participant will be at very low risk (less than 1%) for fainting. Transfer to the emergency room might be needed if the participant fails to improve as expected.
- Effect of Magnetic Stimulation – Effect described on implanted devices (such as pacemakers, deep brain stimulation leads or cochlear implants). To avoid this potential complication, the participant will be excluded from the study if the participant has any metallic implants such as pacemakers, implants, metal rods or hearing aids.
- Childbearing Potential- There may be unknown risks to the fetus. Therefore, women of childbearing age will complete a pregnancy test for the TMS portion of the study at each visit. In order for the women of childbearing age to participate in this study, the participant should avoid becoming pregnant from their first day of most recent menses. A negative pregnancy test does not absolutely prove that a woman is not pregnant. If the female participant thinks that there is a possibility that she might be pregnant, the study team should be notified immediately. Nursing mothers are not eligible for participation in this project. The possibility exists that complications and undesirable side effects, which are unknown at this time, could occur.

EEG:

- A gel paste is used to attach the sensors during EEG which may mildly and briefly irritate the skin on the scalp or face. Hair products cannot be used on the day of testing (or should be washed out prior to testing), which may be inconvenient to the participant.

EMG:

- A gel paste is used to attach the sensors during EMG which may mildly and briefly irritate the skin.

APDM:

- For the measurement of body movement with the APDM, the participant may lose balance or fall while standing with hands on hip and walking a short distance. The study staff will keep a close distance to avoid any falls.

Possible Benefits:

The participant may or may not benefit from taking part in this study. The rTMS may have a short-term benefit on tremor or dystonia, and our goal is to understand the mechanism under which this occurs. The information learned in this study will benefit the neurology and therapy development community. In addition, the information from this study might help researchers develop better treatments using rTMS and EEG to help others with Dystonia and tremor in the future.

Confidentiality

Information collected about the patient will be stored in locked filing cabinets or in computers with security passwords. Only certain people have the legal right to review these research records, and they will protect the secrecy (confidentiality) of these records as much as the law allows. These people include the researchers for this study, certain University of Florida officials, the hospital or clinic (if any) involved in this research, and the Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research). Otherwise the research records will not be released without participant permission unless required by law or a court order.

Researchers will take appropriate steps to protect any information they collect about participants. However, there is a slight risk that information about participants could be revealed inappropriately or accidentally. Depending on the nature of the information such a release could upset or embarrass them, or possibly even affect their insurability or employability.

If the results of this research are published or presented at scientific meetings, patient identity will not be disclosed.

Depression measure and suicide risk

If the Beck Depression Inventory reveals that the patient has feelings of harming themselves, we will refer them to mental health services available at Shands at the University of Florida.

References

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