NCT04916444

Title: Dystonia Treatment With Injections Supplemented By Transcranial Magnetic Stimulation

Document Date: 6/17/2022

IRB Research Protocol

Title: Dystonia Treatment With Injections Supplemented by TMS: the D-TWIST study

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Background: Dystonia is a hyperkinetic movement disorder defined by excessive, involuntary, and often painful muscle contractions.[1,2] The most common form of adult-onset isolated dystonia is cervical dystonia.[3] In addition to pain and abnormal posture, dystonia is associated with non-motor symptoms such as increased rates of depression, anxiety, and cognitive changes. There is also evidence to show clinical and subclinical gait changes in dystonia. [4-8] Currently, the gold standard treatment for dystonia is botulinum toxin (BoNT) injections administered every 12 weeks to affected muscle groups.[9-11] However, these injections can be painful, can be complicated by side effects such as dysphagia and neck weakness, and patients commonly report that the benefits of BoNT do not last the entire 12 weeks.[11] In a retrospective analysis of dystonia patients injected at our center (n = 150), we found the average duration of benefit was about 9.5 weeks, which was similar to reports by other studies.[12,13] Also, BoNT treatment provides only pure symptomatic motor benefits and does not modify the disease pathophysiology.[14-16] Other treatment options such as deep brain stimulation may be effective for some types of dystonia, but it is an invasive procedure and not all patients are appropriate candidates for this surgery.[2,9] Therefore, there is clear merit in exploring other options to potentiate and possibly prolong the benefits of BoNT therapy.

Transcranial magnetic stimulation (TMS) is a painless and non-invasive neuromodulation technique that uses a magnetic field to induce an electric field in the cortex. TMS pulses delivered on a repetitive basis known as repetitive TMS (rTMS) has the ability to modulate dystonia networks and lead to clinical improvements. rTMS delivered at low-frequency (≤ 1 Hz) mimics long-term depression, leading to decreased cortical excitability, while high-frequency TMS (> 5 Hz) mimics long-term potentiation, leading to increased cortical excitability.[10,17] rTMS delivered over multiple sessions has cumulative benefits which last beyond the stimulation period.[9,10] rTMS effects extend beyond the area targeted for stimulation and can influence remote brain regions.

Dystonia is a network disorder involving the motor cortex, premotor cortex, and their connections with other brain regions. The therapeutic role of rTMS in dystonia has been investigated in only a few studies, which employed low-frequency stimulation parameters and found the dorsal premotor cortex (dPMC) as an important brain target for modulation of the dystonia network.[11] These studies mostly focused on patients with arm and hand dystonia, even though cervical dystonia is the most common form of dystonia.[18-21] Furthermore, these studies were small, many involved only a single session of rTMS, the follow-up time period was limited, and they have yet to investigate the interactions between BoNT and rTMS as a potential adjuvant therapy. Finally, rTMS targeted to the dystonia network is likely to influence motor and non-motor symptoms such as depression, anxiety, and cognitive impairment; however clinical studies conducted so far have not assessed non-motor benefits.[17]

The **primary goal** of the proposed study is to determine whether low-frequency rTMS delivered to the dPMC has synergism with BoNT therapy in patients with isolated cervical dystonia. We will determine whether rTMS serves as a therapeutic bridge for early fading of BoNT benefits (**Aim 1**). We will select patients receiving BoNT injections every 12 weeks but endorsing clinical benefits lasting < 9 weeks. We will initiate active versus sham rTMS therapy in a crossover design at 9 weeks after receiving BoNT injections. We will measure the effects at baseline or prior to the first TMS session (T0), immediately after (T1) and 2 weeks after (T2) rTMS (Figure 1). The T2 visit will coincide with their next round of botulinum toxin injections (this study visit will be approximately 12 weeks after their initial BoNT injection. The participants will then undergo the same exact study protocol but will have either active or sham rTMS (whichever treatment they were not assigned to in the first round). As the rTMS therapy requires multiple sessions spanning weeks for cumulative benefits, feasibility

and compliance for completion of therapy can be challenging. We therefore propose an accelerated rTMS protocol which will condense multiple sessions into 4 consecutive days. Accelerated rTMS protocols have shown success and safety in other patient populations[22-24], but have not yet been studied in dystonia. In addition, the crossover design will be feasible because these patients are already traveling to UF clinic for botulinum toxin injections every 12 weeks as part of their standard of care, so most if not all will live within an acceptable driving distance for them to complete the protocol.

In addition to clinical outcomes, we will investigate the physiological changes underlying the clinical effects (**Aim 2**). Single-pulse and paired-pulse studies in patients with dystonia have revealed inhibitory dysfunction, particularly increased motor evoked potential (MEP), prolonged cortical silent period (CSP), and reduced short intracortical inhibition (SICI).[25-30] These findings implicate a primary dysfunction of the motor cortex. To further understand the motor cortex functions, we recently employed high-density electroencephalogram (HD-EEG) techniques. We found there was an impaired cortical desynchronization in the alpha and beta bands during voluntary movement in patients with cervical dystonia.[31]

OBJECTIVES/SPECIFIC AIMS:

Specific Aim #1: Determine the Clinical effects of rTMS combined with BoNT in isolated cervical dystonia. We will determine the clinical effects of active vs. sham rTMS on motor, non-motor, and gait symptoms. We will examine the motor effects with the standardized Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), mood with the Beck Depression Inventory, cognition with the Wisconsin Card Sorting Task and Trail Making Test, and gait with the instrumented Zeno walkway system. We hypothesize there will be greater improvement in the motor (primary outcome), nonmotor, and gait measures (secondary outcomes) at T1, and T2 compared to baseline in the active rTMS group compared to the sham rTMS group.

Specific Aim #2: Determine the Physiological effects of rTMS combined with BoNT in isolated cervical dystonia. We will determine the physiological effects of active vs. sham rTMS using TMS and EEG techniques. We will examine the cortical excitability with established TMS parameters including MEP, CSP, and SICI, and we will examine cortical desynchronization of alpha and beta band with resting state HD-EEG. We hypothesize that the change in TMS measures and EEG measures at T1, and T2 compared to baseline will significantly improve in the active rTMS group compared to the sham rTMS group and will correlate with the clinical improvements as outlined in specific Aim #1.

RESEARCH PLAN AND METHODOLOGY: Patients with a diagnosis of isolated cervical dystonia receiving BoNT every 12 weeks at our movement disorders center will be enrolled. Diagnosis of cervical dystonia will be established in accordance with the Consensus Statement of the Movement Disorders Society.[1]

Inclusion Criteria: patients 18-85 years of age who receive regular BoNT scheduled every 12 weeks, on stable optimized doses but with reported benefits lasting ≤ 9 weeks for 2 consecutive cycles. Patents followed at our center routinely fill out a self-reported form to document the duration of benefits perceived with BoNT therapy. Participants will be allowed to continue oral medications that they are taking for dystonia concurrently and will be encouraged to continue this regimen throughout the duration of the study .
Exclusion Criteria: 1) Presence of metallic objects or neurostimulators in the brain (including the following: cochlear implants, implanted electrodes/stimulators such as deep brain stimulators and vagus nerve stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes) , 2) pregnancy, 3) history of active seizures or epilepsy, 4) patients with severe scoliosis or other gait impairment that will preclude them from participating in gait evaluation.

Enrollment: Our target is to enroll 10 total patients in the study in a crossover design, with all 10 patients receiving both active and sham rTMS in blinded, random order. In order to enroll 10, we will need to screen more than that number. We anticipate that we will need to screen 20 patients in order to find 10 that are eligible for enrollment. Of those 20, we anticipate that 10 will enroll but later choose not participate in the study.

IRB approved informed consent will be obtained. The study procedures will be explained, and subjects will have a detailed medical history and neurological examination. Patients will be randomly assigned to receive either active or sham stimulation first (S1), and will then crossover and switch to the other treatment type during the second session (S2). Patients will have primary and secondary outcome measures performed at three time points: Baseline (T0), following rTMS (T1), and 2 weeks after rTMS (T2) (Figure 1). Patients will have the next round of regularly scheduled botulinum toxin injections during the T2 study visit, after the outcome measures have been obtained. Then the entire study protocol will be performed again but the patients will undergo either active or sham rTMS during S2 (whichever option they were not exposed to during S1). The study protocol will take place over approximately 24 weeks. Details of specific parts of the protocol are included below.

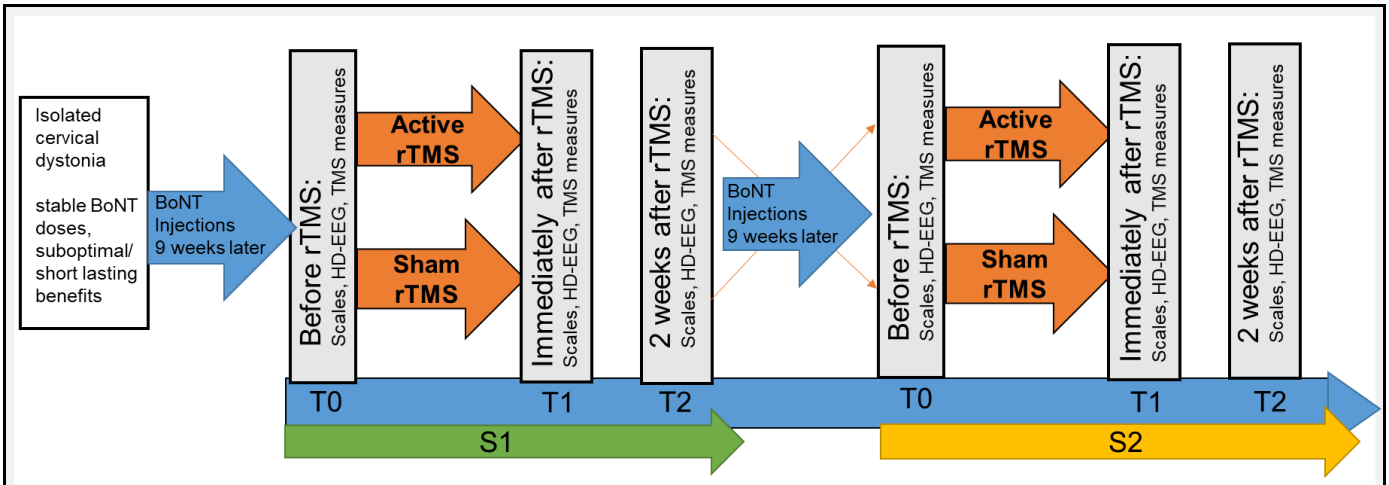

Figure 1: Study design for cervical dystonia patients reporting botulinum toxin injection benefits lasting ≤ 9 weeks, will be randomized to two groups of active and sham rTMS as part of the first session (S1) and have outcome measure obtained at baseline/9 weeks after BoNT (S1:T0), after the full rTMS protocol (S1:T1), and 2 weeks after rTMS (S1:T2). At the T2 visit, patients will be due for their next round of BoNT and will receive it at that time. Patients will have S2:T0 performed 9 weeks following this round of BoNT and will crossover into either active or sham rTMS (whichever condition they did not undergo in S1). Outcomes will be measured immediately following rTMS (S2:T1) and 2 weeks after rTMS (S2:T2).

Primary Outcome: Motor symptoms of dystonia will be measured with TWSTRS; a widely accepted composite rating scale for cervical dystonia with subscales for clinical severity, functional disability, and associated pain. We will record videos of subjects at baseline and follow-up time points, which will be scored by two independent blinded raters.

Secondary Outcomes: Non-motor symptoms will be measured as follows: mood with the Beck Depression Inventory (BDI) and cognitive tasks as measured by the Wisconsin Card Sorting Task (WCST) and Trail Making Test (TMT); gait with Zeno walkways system for temporal parameters (stance time, double support time, stride time, and cadence), spatial parameters (stride length, step width, step length, step asymmetry), and the dynamic stability index (ratio between single and double support time)[4,5]; physiological outcomes will be measured with standard procedures for TMS based MEP, CSP, and SICI[25-30] and HD-EEG based power of alpha and beta bands during resting state.[31]

Randomization: A random number generator will be used to assign patients to active or sham stimulation during the S1 time period. If the number is even, the patient will be assigned active stimulation. If the number is odd, the patient will be assigned sham stimulation. The study team member who makes these assignments will be aware of which patients are receiving active or sham stimulation but will be different from the blinded reviewer. The blinded reviewer will be unaware of the patient's assignment to active or sham stimulation. Following crossover, the patients will undergo whichever treatment condition (active or sham) they were not exposed to during S1.

rTMS protocol: rTMS will be delivered using a NeuroStar TMS therapy system (Neuronetics, Malvern, PA). The resting motor threshold (RMT) will be defined as the lowest stimulation intensity required to evoke a 50 μV potential in a target muscle (i.e. first dorsal interosseus muscle/FDI). A figure of eight coil will be used to deliver the stimulation. Patients will be seated in a comfortable reclined chair. The dPMC target will be defined as 1 cm medial and 2 cm anterior to the site of RMT acquisition.[11] The rTMS protocol will be as follows: each session will consist of 1-Hz rTMS over the dPMC for 30 minutes (1800 pulses) at 90% of the RMT. Patients will receive 4 sessions per day for 4 consecutive days with a 10-minute break between each session. Daily duration of the rTMS protocol, including breaks, will last approximately 160 minutes. Constant coil position will be continuously monitored during the experiment. During rTMS, all participants will wear earplugs in order to protect the ears from the acoustic artefact associated with the discharge of the stimulation coil.

Sham protocol: Participants will undergo the same procedure for identifying target location and RMT used in patients receiving real rTMS. Simulated rTMS will be administered using a NeuroStar sham coil, which produces discharge noise and vibration without stimulating the cerebral cortex. This technique has been suggested to provide more effective blinding compared to other methods use in previous controlled studies.[17] Although the physician administering TMS will be aware of the status of the subject in terms of real TMS versus sham TMS, this physician will play no role in any of the outcome measures, and will not be present during any of the outcome measure assessments. Similarly, the investigator who performs the outcome measures will not be present during any of the TMS sessions, and therefore will remain blinded to the status of the patients with respect to real rTMS versus sham rTMS.

Single and paired-pulse TMS paradigms: A MagStim BiStim device (Whitland, UK) will be used for the single and paired-pulse TMS paradigms. These will be followed per established protocols in the literature (Figure 2 A and C).[10] A single-pulse of TMS will be targeted over the motor cortex to generate a motor evoked potential (MEP), which can be captured on EMG. The rest of the EMG will be analyzed to assess the time between the TMS pulse and the MEP (also known as the latency) and the amount of time muscle activity remains silent following the MEP (also known as the cortical silent period). In a paired-pulse TMS paradigm, a subthreshold pulse will be provided followed by an interstimulus interval and then subsequent delivery of a suprathreshold pulse. When the interstimulus interval is short (1-4 msec), the ratio of MEP amplitudes produced by these two pulses is known as short interval intracortical inhibition (SICI).

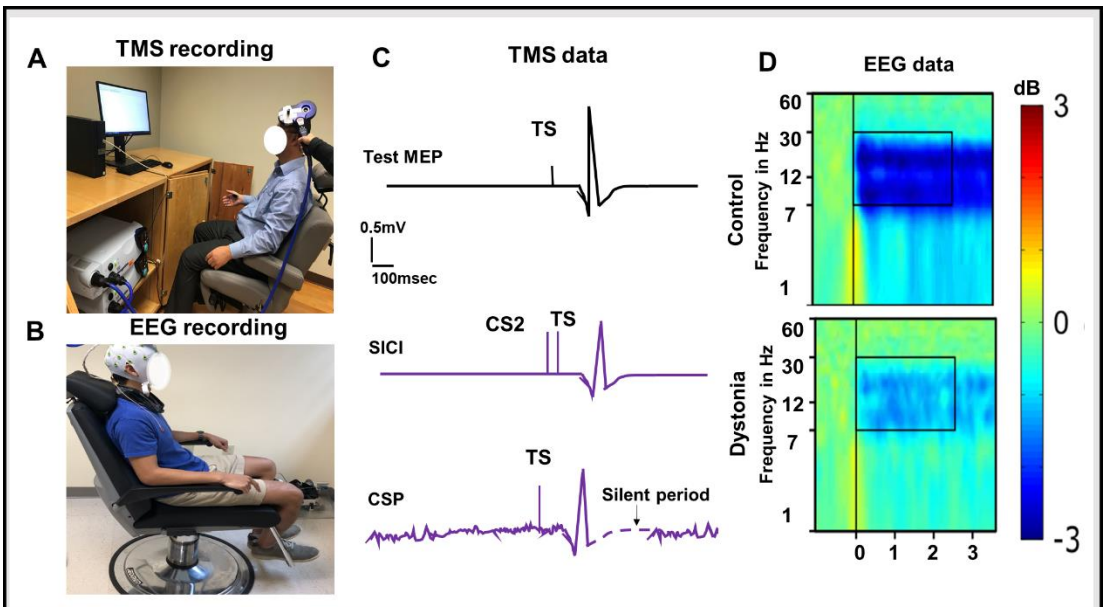

Figure 2: A) TMS setup, 1. Magstim TMS machine; 2. figure-of-8 TMS coil placed over the motor cortex; 3. EMG recording from contralateral hand muscle; B) EEG Cap for high density recordings at rest C) TMS parameters of motor evoked potential (MEP) with single pulse TMS, short interval intracortical inhibition (SICI) and cortical spinal period (CSP) with paired pulse TMS TS is test stimulus and CS is conditioning stimulus D) Event-related spectral perturbations (ERSP) time-frequency plots for dystonia vs healthy controls, A box encompassing time 0 to 2.5 seconds and frequency 7 to 30 Hz is placed to show where statistical analysis will be conducted.

EEG protocol: High-Density EEG using 128 electrodes as the setup will be implemented. Each EEG session should last about 1 hour. Patients will be seated comfortably in a chair and a cap will be stretched across the scalp. This cap has 128 contacts where the electrodes will be connected using biosoluble glue. The electrodes will be placed appropriately by a clinician or technician trained to place the EEG electrodes. The patient's electrical activity will be recorded under two conditions: at rest and with maximal

range of motion/excursion in six directions: up, down, left, right, left shoulder, right shoulder. Patients will also be instructed to perform arm movements while the EEG is recording. A sensor such as the Delsys system will be used to measure the patient's motion at the neck and head throughout this procedure. This portion of the study will be videotaped (Figure 2B and D).

Safety: Since the most important safety concern with rTMS is the possibility of seizure, participants with active seizure disorder or those at increased risk of seizure will be excluded. Low frequency protocols carry less risk of seizure as compared to high frequency protocols given that high frequency generates cortical excitability.[32] In spite of the theoretically increased risk of seizure in accelerated rTMS protocols, several accelerated high-frequency protocols have been safely performed in other patient populations and have been tolerated well by patients without evidence of increased adverse events.[22-24] The majority of these accelerated protocols are high-frequency stimulation, whereas our protocol calls for low-frequency stimulation which actually has an inhibitory effect and may actually be protective against seizures. A fuller review of accelerated rTMS protocols in a variety of different patient populations, with all adverse events listed can be found in the supplementary file included with this submission- it should be noted that the seizure risk was not greater in accelerated rTMS protocols compared to standard rTMS protocols. Other mild and transient side effects that participants may experience secondary to TMS include transient eye pain, toothache, muscle twitch, facial pain, neck stiffness, and pain or discomfort at the application site and skin.

Depression measure and suicide risk: If the Beck Depression Inventory reveals that the patient has feelings of harming themselves (Question 9 score 2 or above), we will refer them to mental health services available at Shands at the University of Florida.

Clinical Assessments:

Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS): This is an objective scale evaluating patients on a variety of features including maximal excursion, duration, effects of sensory trick, shoulder elevation, range of motion, and time. This portion of the study will be videotaped.

Beck Depression Inventory (BDI): This is a 21-question survey evaluating depression in patients on a 0 to 3 scale.

Trail-Making Test: This is a 2-part evaluation in which patients are instructed to connect circles in ascending numerical order and are scored on how quickly they are able to complete the task.

Wisconsin Card Sorting Test (WCST): This is a cognitive task that asks patients to sort cards based on color, number, and shape.

Gait Assessment: Patients will be asked to walk across the Zeno walkways system for temporal parameters (stance time, double support time, stride time, and cadence), spatial parameters (stride length, step width, step length, step asymmetry), and the dynamic stability index (ratio between single and double support time). This portion of the study will be videotaped.

Patient will also have HD-EEG and TMS measures (MEP, CSP, and SICI) performed as described above.

Patients will have primary and secondary outcome measures performed at six timepoints: Baseline (T0), following rTMS (T1), and 2 weeks following rTMS (T2) during session 1 (S1) and baseline (T0), following rTMS (T1), and 2 weeks following rTMS (T2) during session 2 (S2) (Figure 1). The study protocol will take place over approximately 24 weeks. All events related to the study procedure will take place within +/- 14 days of the expected timeline, with more details below (Table 1).

Table 1. Timeline of study events and expected study activities at each timepoint.

	Session	S1					S2				
Study Events (to occur +/- 14 days)	**Screen-ing**	**Botox-Week 0**	**Baseline (T0)-Week 9**	**rTMS protocol (4 days)**	**Post-TMS (T1)-Week 10**	**2 weeks post-TMS (T2)-Week 12**	**Botox-Week 12**	**Baseline (T0)-Week 21**	**rTMS protocol (4 days)**	**Post-TMS (T1)-Week 22**	**2 weeks Post-TMS (T2)-Week 24**
Informed Consent											
Medical History											
Neurologic Exam											
Pregnancy Test (if woman of childbearing age)											
Demographics											
Botox											
Active or Sham rTMS											
TWSTRS											
BDI											
Trail Making Test											
WCST											
MEP											
CSP											
SICI											
Gait assessment											
HD-EEG											
Study Compensation											

Compensation: Participants who live a minimum of 50 miles from Gainesville will be offered a 4-night hotel stay of up to $100 per night in Gainesville (for 4 nights) so that they can complete the 5 consecutive days at the S1:T1 and S2:T1 timepoints. That way they can complete this portion of the study without having to travel back to their home each night. This will be paid in the form of gift cards at the time the patient and family are staying at the hotel ($400 for the S1 time period and $400 for the S2 time period). In addition, participants will be compensated up to $300 ($150 for gas and $150 for food) during their visits to the Fixel Center/UF related to participation in this study. This will be prorated so that they will receive $50 in gift cards ($25 for gas and $25 for food) in 6 equal installments at each of the outcome measure timepoints: S1:T0, S1:T1, S1:T2, S2:T0, S2:T1, and S2:T2. Participants will also be compensated $150 for taking part in the study (for their time). This compensation will be prorated, so that patients will receive $25 in gift cards in 6 equal installments, correlating with the S1:T0, S1:T1, S1:T2, S2:T0, S2:T1, and S2:T2 outcome timepoints.

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. 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. In addition, the DSMC will meet after the first two patients in the study have completed the protocol to ensure safety and tolerability parameters are being met. Coralie de Hemptinne, PhD, Ashley Rawls MD, and Aparna Wagle Shukla MD will monitor the safety of the project yearly. Dr. Rawls will serve as an independent health professional on the Data Safety Monitoring Committee.

Location: The clinical portions of the study will be performed at the Fixel Neurological Institute; patients will have the clinical outcome measures collected in a clinic or research room. Patients will have the clinical outcome measures collected in a clinic or research room. The NeuroStar TMS machine is located in a separate TMS room within the Fixel Neurologic Institute. The Zeno gait walkway system is also located in the Fixel Neurologic Institute. Other devices necessary to complete the study inclue these portable devices which will reside in the TMS room during the study procedure:

EMG system: Bagnoli™ Desktop EMG system (Delsys, Inc., Boston, Massachusetts). It includes four surface electrodes to detect muscle movement
EEG system: ActiveTwo system (Biosemi, Amsterdam, Netherlands). It has a cap with electrodes in a preconfigured montage, using 128 Ag-AgCl electrodes.

Possible Discomforts and Risks: There are some possible discomforts and risks for participants taking part in this study, most of which are mild or transiently related to the study protocol and will abate afterwards.

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. Since FDA clearance of TMS, 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 – The NeuroStar TMS Therapy System is contraindicated for use in patients who have conductive, ferromagnetic, or other magnetic-sensitive metals implanted in their head within 30 cm of the treatment coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes. Failure to follow this restriction could result in serious injury or death. The NeuroStar TMS Therapy System is contraindicated for use in patients who have active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators. Contraindicated use could result in serious injury or death. To avoid these complications, participants with any of the above listed implanted objects will be excluded from this

study.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.

Possible Benefits: The participant may or may not benefit from taking part in the study. All participants will continue receiving botulinum toxin injections every 12 weeks as part of their standard of care. All patients will receive both active and sham rTMS; since the active rTMS is hypothesized to augment the effects of botulinum toxin injections, patients may experience further reduction in symptoms or sustained response to botulinum toxin. The information gathered from this study will benefit the neurology department and the larger research community as we continue to seek the most efficacious treatments for cervical dystonia.

Regulatory Approval and Statistics: The study will be approved by the University of Florida Institutional Review Board, and all subjects will provide written informed consent. The study is highly feasible given the relatively large number of patients with cervical dystonia that receive botulinum toxin injections on a regular basis. This is a pilot study so it has not been powered for statistical significance. We will use descriptive statistics and ANOVA to run analysis on the data that has been collected.

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.

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