Title: Combined therapy with rTMS and botulinum toxin in primary cervical dystonia

Principal Investigator: Aparna Wagle Shukla, MD

Sub-Investigator: Wei Hu, MD

Primary cervical dystonia (PCD) is the most common form of focal dystonia.[1] PCD is frequently reported as a source of disability,[2] decreased quality of life,[3] and social stigma.[4] Botulinum toxin (BoNT) is the gold standard treatment for PCD (Class I evidence, Level A recommendations).[4] This therapy has the advantage of avoiding central side effects such as sedation, cognitive clouding, and balance impairment, which are risks related to oral pharmacotherapy such as anticholinergic medications. Although the current standard of care is injecting no more frequently than every 12 weeks to reduce the risk of developing immunity, patients commonly report fading of benefits sooner than 12 weeks following the injection.[5] We conducted a retrospective analysis of PCD patients injected with BoNT at our center (n=150). We found the average duration of benefits from BoNT injections was about 9.5 weeks which was also reported by other studies.[5] Also, BoNT treatment is known to provide only pure symptomatic benefits and does not seem to modify the disease pathophysiology.[3,4,6] Thus although BoNT therapy is the first-line approach for treatment of PCD, in many patients it provides only suboptimal benefits. Therefore there is clearly a merit in exploring other options to potentiate and possibly prolong the benefits of BoNT therapy.

We propose to use repetitive transcranial magnetic stimulation (rTMS) therapy as an adjunctive therapy in combination with BoNT injections as a novel approach to treat PCD. rTMS refers to the application of transcranial magnetic stimulation (TMS) pulses to a specific target at predefined stimulation parameters.[7-9] The fundamental mechanism of action for rTMS is modulation of brain excitability. rTMS therapy has shown beneficial results in many neurological and psychiatric conditions.[7-10] rTMS therapy is FDA approved for treatment of medication refractory depression.[7,11] rTMS at frequencies of 5-Hz and higher has been found to transiently enhance excitability, [7,12] whereas rTMS at frequencies of 1-Hz and lower has been found to depress cortical excitability.[7,13] Repeated sessions of rTMS therapy have been demonstrated to induce cumulative persistent benefits that can last weeks after the conclusion of the rTMS sessions. For example, in a recent double blind randomized controlled study, low frequency rTMS delivered over eight weeks to Parkinson's disease patients showed positive clinical benefits that lasted for 12 weeks beyond the last rTMS session.[14]

The **primary goal** of this study is to compare standard treatment with BoNT versus BoNT combined with a one week course of rTMS. Although the pathophysiology of dystonia has been traditionally regarded as a disorder of the basal ganglia-motor cortex network, there is increasing evidence to show that the cerebellum plays an important role. The cerebellum in dystonia has been found to be defective both at a structural and functional levels.[15] Several neuroimaging studies have shown an abnormally increased activity in the cerebellum.[16-21] High frequency rTMS of the cerebellum was found to modulate the sensorimotor plasticity response in dystonia.[8-10] Thus there is now significant evidence to show that cerebellum in the brain plays an important role in pathophysiology of dystonia. The cerebellum has been found to be defective both at a structural and functional levels. We therefore plan to use cerebellum as our target of stimulation in our study.

The **central hypothesis** of this study is that rTMS therapy in PCD can potentiate the effects of BoNT injections. With the current standard treatment, the peak-dose benefits seen with BoNT are seen at about 4-6 weeks after the administration of injections. We plan to introduce a 1 week course of rTMS around 2-8 weeks before or after BoNT or T1). We may examine the effects of combined therapy at around 10 weeks after BoNT (T2) and at around12 weeks after BoNT (T3) injections follow-up (Figure A). We will record the clinical outcome with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), a standardized validated rating scale for PCD. We will also measure the physiological effects at these time points with transcranial magnetic stimulation (TMS) technique, a useful tool to understand the brain physiology. We will measure the effects of rTMS on cerebellar excitability with a well-established TMS parameter referred to as cerebellar inhibition (CBI). As mentioned in aforementioned section, rTMS delivered at 1 Hz and below inhibits the brain

and when delivered at frequencies greater than 5 Hz, [7,11-13] it excites the brain. Based on previous imaging studies that showed increased activation of cerebellum in dystonia, [16-21,28] we plan to use low frequency rTMS to achieve inhibition of cerebellum and improvement of symptoms.

It is reasonable to be concerned that the alongside the effects of low frequency rTMS on excitatory loops, the inhibitory loops in the cerebellum could as well be further inhibited by rTMS. We are therefore planning to include the cerebello-cortical inhibition circuit to determine the effects of rTMS on an inhibitory loop.

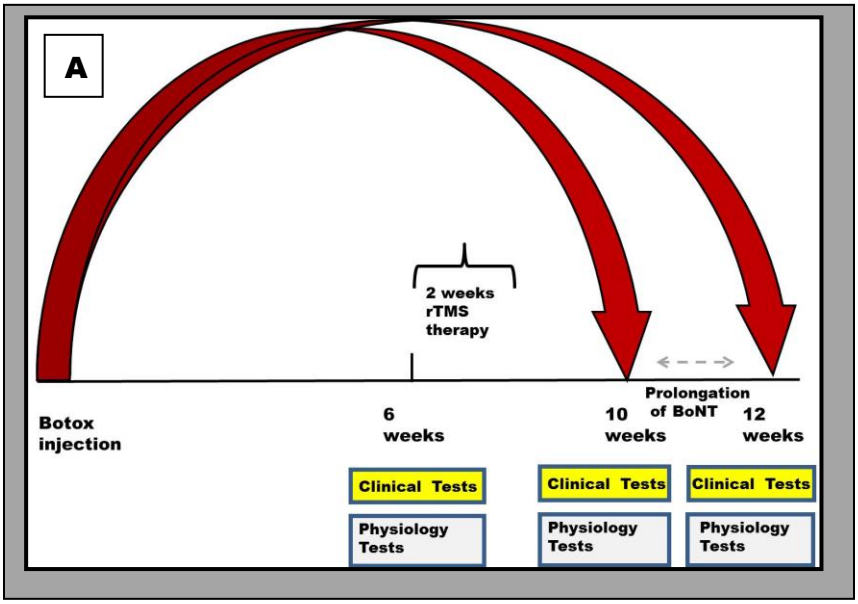
SPECIFIC AIM 1: Clinical impact of rTMS therapy in PCD.

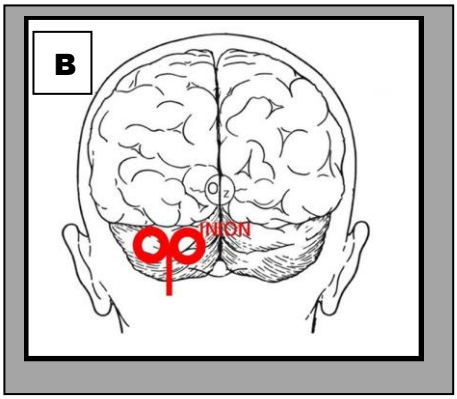
We will determine the clinical effects of 1-Hz rTMS therapy of the cerebellum when combined with BoNT injections in PCD. Comparisons will be drawn in the clinical scoring of TWSTRS (blinded videotape ratings) between T1 (around 6 weeks after BoNT injections or the start of rTMS therapy), T2 (around 10 weeks after) and T3 (around 12 weeks after or at the time of next BoNT injection) assessments. We hypothesize benefits seen at T2 follow-up compared to T1 will be greater in the group receiving combined rTMS and BoNT therapy compared with standard BoNT alone. Similar effects will be seen at T3 follow-up but they will be reduced in magnitude. (Figure C)

SPECIFIC AIM 2: Physiological impact of rTMS therapy in PCD

Aim 2a: We will determine the physiological effects of 1-Hz rTMS therapy when combined with BoNT injections in PCD. We will record the time course of effects on cerebellar inhibition (CBI) at T1, T2 and T3 follow-ups by MAGSTIM system. We hypothesize that compared to T1, CBI will be reduced and reach physiological levels at T2 follow-up. CBI will continue to remain at physiological levels at T3 follow-up though to a lesser extent.

Aim 2b: We will determine if the physiological effects of 1-Hz rTMS therapy as reflected in CBI, will correlate with the clinical scoring of PCD symptoms. We hypothesize that the change in CBI measure at T2 and T3 follow-ups will show positive correlation with the improvement in PCD symptoms at these time points.





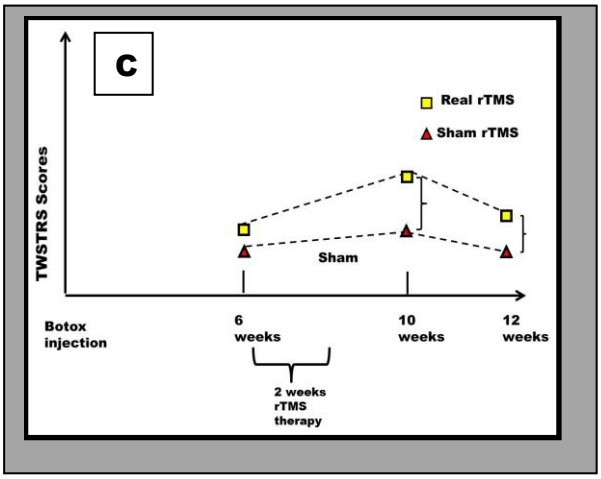


Figure: **A,** rTMS therapy will be administered in the period 6-8 weeks after the BoNT injections. The clinical tests will include TWSTRS scores. The physiological tests will include CBI measured with TMS. **B,** rTMS therapy will be delivered over the cerebellum **C,** The anticipated outcomes are shown with line graphs, the main outcome is clinical difference between real rTMS arm and sham rTMS arm at around 10 and 12 weeks.

STUDY DESIGN: Subjects receiving BoNT therapy for a diagnosis of PCD will be enrolled. Diagnosis of PCD will be established in accordance with the Consensus Statement of the Movement Disorders Society.[27] In this two year study, we plan to recruit **20 subjects with PCD** in the age range 21–80 years. Subjects followed at our center regularly fill out a self-reported form to document the duration of benefits they perceive with BoNT therapy. We will enroll subjects who report benefits lasting 10 weeks or less only (suboptimal benefits with standard care). Specifically, our inclusion criteria are: 1) Diagnosis of PCD according to the Consensus Statement of the Movement Disorders Society; 2) Report benefits of BoNT lasting 10 weeks or less only. We will exclude subjects with 1) pregnancy; 2) active seizure disorder 3) presence of a metallic body such as pacemaker, implants, metal rods and hearing aid. We will also identify subjects who meet inclusion/exclusion criteria from the IRB approved database (#416-2002). These subjects have consented to be contacted for future research. We will enroll **10 healthy** age and sex-matched controls for normative electrophysiological data. Controls will be recruited through fliers placed across the campus. Specifically, our inclusion criteria are: 1) There is no history of any neurological disorders; 2) Neurological exams are unremarkable. We will exclude subjects with 1) pregnancy; 2) any neurological disorders 3) presence of a metallic body such as pacemaker, implants, metal rods and hearing aid.

Eligible subjects will be invited to an introductory session. We will obtain IRB approved informed consent. Subjects will be explained in detail about the procedures outlined for the study. Subjects will have a detailed medical history and neurological examination using the NINDS Common Data Elements. Subjects will be randomized to receive BoNT therapy combined with real or sham rTMS (1:1, 10 subjects in each arm). At our center, PCD subjects are scheduled for BoNT injections approximately every 12 weeks. rTMS therapy will be administered in the period around 2-8 weeks before or after the BoNT injections. 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.

Outcome measures. The clinical outcome will be measured with Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The TWSTRS is a widely accepted composite rating scale for PCD with subscales for clinical severity, functional disability, and associated pain. Studies evaluating the clinimetric properties of TWSTRS have demonstrated substantial reliability, validity, and responsiveness to change following therapeutic intervention. It is the most commonly employed outcome measure in PCD trials and has practical applicability in a clinical setting. Also, we will administer the Craniocervical Dystonia Questionnaire Description for quality of life assessment. The Craniocervical Dystonia Questionnaire (CDQ-24) is a patient-rated health related quality of life (HR-QoL) measure for craniocervical dystonia. It has been validated for use in clinical research. The CDQ-24 measures the impact of Craniocervical Dystonia on 5 HR-QoL domains. It is composed of 24 items, forming 5 subscales: stigma, emotional well-being, pain, activities of daily living, and social/ family life. Items are rated on a 5-point scale.[23] Each item consists of five statements representing increasing severity of impairment, scored from 0 to 4. Subjects will be instructed to indicate how they have felt during the past two weeks because of dystonia by selecting one of the five statements for each item. Subjects will also rate their symptoms before and after stimulation using a 7-point nominal scale: 1) excellent, 2) very good, 3) good, 4) average, 5) slightly worse than usual, 6) bad or 7) very bad.

We will record videos of subjects at T1, and possibly at T2 and T3 time points which will be scored by two independent blinded raters (excluding control patients). We will obtain IRB approval to consent subjects in order to obtain videos of all subjects (excluding control subjects). The physiological outcome will be measured with TMS (CBI measure).We will also obtain MRI scan before and after rTMS therapy.

Brain Structure Measures: We will be using the research dedicated 3T Phillips or 3T Siemens MRI scanners in the McKnight Brain Institute to obtain diffusion tensor imaging, T1 weighted, and T2 weighted images. [21] We will be using the 32 channel head coil (Phillips) or 64 channel head coil (Siemens) for data acquisition.

Brain Function Measures: We will be using the research dedicated 3T Phillips or 3T Siemens MRI scanners at the McKnight Brain Institute to obtain functional magnetic resonance imaging (fMRI) data during the production of grip force production tasks[22-24]. Participants will use their hand to squeeze an MRI compatible

grip force transducer in the MRI unit. This is a fiber optic transducer that is fully compatible with MRI. When producing force, the participants will view the amount of force they generate when viewing the visual feedback on a MRI compatible visual display while lying inside the scanner.

RTMS THERAPY:

Real stimulation: Repetitive-TMS will be delivered over each cerebellar hemisphere, using a NeuroStar TMS therapy system (Neuronetics, Malvern, PA, USA).[22] This coil, delivering TMS pulses to the patient's brain, will be positioned over a point that is 3 cm lateral to the inion on the line joining the inion and the external auditory meatus. The coil position will be marked on the skin. 900 pulses will be delivered consecutively to each side with a frequency of 1 Hz and at an intensity of 90% of the resting motor threshold (RMT) for a total duration of 15 min for each cerebellar hemisphere. The 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 in our case). Constant coil position will be continuously monitored during the experiment. 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. A similar protocol will be observed for the contralateral cerebellum.

Sham Stimulation*:* Patients will undergo the same procedure for identifying stimulus location used in patients receiving real rTMS. Simulated rTMS will be administered using NeuroStar TMS therapy system 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.[23]

Safety of rTMS*:* Repetitive TMS can have undesired side effects.[24] The proposed study will use TMS parameters well within the published safety guidelines adopted by the International Federation for Clinical Neurophysiology and subsequently updated.[25,26] We will conduct careful monitoring of the participants and follow all recommended precautions for the application of TMS.

Data Safety Monitoring Plan

The principal investigator monitors the patient safety and data collection of each study visit. If she feels there is possible harm to subject safety or the possibility of, any harm due to something new that was learned during the study, she will convene a multi-disciplinary committee of at least 2 health professionals to perform a thorough review of the study details.

Regulatory Approval, Statistics, Time Line

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 large number of PCD subjects seen at UF and the considerable expertise. Statistical analyses will be performed using commercially available statistical software (SPSS, version 19.0; SPSS, Inc., Chicago, Illinois). We aim to enroll 20 subjects for this pilot study, and 10 control subjects. For Aim1 and 2a, we will conduct a mixed model analysis using time and stimulation arm as repeated factors adjusted for baseline values, and subjects as the random factor. The model will include 2 factors: treatment (2 levels: real vs sham) and time (3 levels: T1, T1, and T3). The 2-tailed significance level will be set at 0.05 For Aim 2b, we will use Spearman correlation test to determine the relation between the change in CBI at T2 compared to that at T1 and change in CBI at T3 compared to that at T1. With an expected difference of 30% in TWSTRS scores at 10 weeks between the two arms (real and sham rTMS), a standard deviation of 20%, type I error of 5% and power of 80%, the necessary sample size for each group is ten completers.

TIME AND EVENTS TABLE

Description	Screening	rTMS V1	rTMS V2	rTMS V3	rTMS V4	rTMS V5	10 wk FU*	12wk FU*
Consent	X							
Neurological Exam	X							
Med History	X							
Inclusion/Excl.	X							
Botox Injection (SOC)	X							
Randomization	X							
MRI		X				X		
rTMS (real/shame)		X	X	X	X	X		
Determine Threshold	X							
Videotape		X				X	X	X
Blinded Rater Eval		X				X	X	X
Urine pregnancy	X							
CDQ 24	X					X	X	X
Clinical Assessments								
TWSTRS		X				X	X	X

Physiological Tests								
CBI measured with TMS	X					X	X	X

*optional

References:

1. Fahn S (Ed): Movement disorders 2. London: Buttersworth; 1987.

2. Tarsy D, Simon DK, Dystonia. N Engl J Med 2006, 355:818–829.

3. Phukan J, Albanese A, Gasser T, Warner T. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. Lancet Neurol. 2011;10:1074-85.

4. Jankovic J. Treatment of dystonia. Lancet Neurol. 2006;5:864-72.

5. Dressler D, Tacik P, Adib Saberi F. Botulinum toxin therapy of cervical dystonia: duration of therapeutic effects.J Neural Transm. 2014 in press

6. Thenganatt MA, Jankovic J: Treatment of dystonia. Neurotherapeutics 2014;11:139-52.

7. Hallett M. Transcranial magnetic stimulation: A primer. Neuron 2007;55:187-199.

8. Lefaucheur JP, Andre-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014.

9. Wagle Shukla A, Vaillancourt DE. Treatment and physiology in parkinson's disease and dystonia: Using transcranial magnetic stimulation to uncover the mechanisms of action. Curr Neurol Neurosci Rep 2014;14:449

10. Edwards MJ, Talelli P, Rothwell JC. Clinical applications of transcranial magnetic stimulation in patients with movement disorders.Lancet Neurol. 2008;7:827-40.

11. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives.Lancet. 2012;379:1045-55.

12. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117 (Pt 4):847-858.

13. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398-1403.

14. Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y, Research Committee on rTMS Treatment of Parkinson's Disease. Supplementary motor area stimulation for parkinson disease: A randomized controlled study. Neurology 2013;80:1400-05.

15. Delmaire C, Vidailhet M, Elbaz A, Bourdain F, Bleton JP, Sangla S, Meunier S, Terrier A, Lehéricy S. Structural abnormalities in the cerebellum and sensorimotor circuit in writer's cramp.
Neurology. 2007;69:376-80.

16. Hubsch C, Roze E, Popa T, Russo M, Balachandran A, Pradeep S, Mueller F, Brochard V, Quartarone A, Degos B, Vidailhet M, Kishore A, Meunier S. Defective cerebellar control of cortical plasticity in writer's cramp. Brain. 2013;136:2050-62.

17. Galardi G, Perani D, Grassi F, Bressi S, Amadio S, Antoni M. Basal ganglia and thalamo-cortical hypermetabolism in patients with spasmodic torticollis. Acta Neurol Scand 1996;94:172-6.

18. Odergren T, Stone-Elander S, Ingvar M. Cerebral and cerebellar activation in correlation to the action-induced dystonia in writer's cramp. Mov Disord 1998;13:497-508

19. Hutchinson M, Nakamura T, Moeller JR, Antonini A, Belakhlef A, Dhawan V, The metabolic topography of essential blepharospasm: a focal dystonia with general implications. Neurology 2000;55:673-7.

20. Preibisch C, Berg D, Hofmann E, Solymosi L, Naumann M. Cerebral activation patterns in patients with writer's cramp: a functional magnetic resonance imaging study. J Neurol 2001;248:7-10.

21. Hu XY, Wang L, Liu H, Zhang SZ. Functional magnetic resonance imaging study of writer's cramp. Chin Med J (Engl) 2006;119:1263-71.

22. http://www.magstim.com/transcranial-magnetic-stimulation/magstim-bistim

23. Rossi S, Ferro M, Cincotta M, Ulivelli M, Bartalini S, Miniussi C, Giovannelli F, Passero S. A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). Clin Neurophysiol. 2007;118:709-16.

24. Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A. Safety of rTMS to non-motor cortical areas in healthy participants and patients.Clin Neurophysiol. 2006;117:455-71.

25. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008-39.

26. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1998;108:1-16.

27. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and Classification of Dystonia: A Consensus Update. Mov Disord. 2013;28:863-73.

28. Prudente CN, Hess EJ, Jinnah HA. Dystonia as a network disorder: what is the role of the cerebellum? Neuroscience. 2014, 28;260:23-35.