Title: *rTMS therapy for primary orthostatic tremor: A novel treatment approach*

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Investigators:

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BACKGROUND AND SIGNIFICANCE:

Primary orthostatic tremor is a rare progressive functionally disabling tremor disorder. The characteristic features of POT are symptoms of unsteadiness in legs reported by patients when they are standing and improvement of symptoms upon walking and sitting. POT tremors recorded on surface electromyography (EMG) reveal distinct high frequency bursts of 13-18 Hz tremors in the leg muscles.[2] POT was first described in 1984 at the University of Florida.[3] Since then several clinical descriptions have been published however despite this knowledge for thirty years, treatment opportunities for POT have remained poor. Several medications have been tried, but the results have been disappointing. Pharmacological therapies such as propranolol, clonazepam and gabapentin have been tried however they have shown only limited success.[1] Thalamic deep brain stimulation (DBS) surgery, which is an invasive therapy approved by the FDA for treatment of essential tremor, was recently investigated in POT but the early results have only been partially successful.[4, 5] Therefore there is a clear merit in continuing efforts to explore and investigate novel treatment modalities.

Although the pathophysiology of POT is not completely elucidated, several studies have suggested that the cerebellum is the source of primary pathology. In clinical descriptions, POT has been observed to be associated with clinical features of cerebellar dysfunction such as dysmetria and gait ataxia.[6,7] Positron emission tomography (PET) imaging has shown an increased activation of bilateral cerebellum related either to a mismatch between the peripheral afferent and the cerebellar efferent traffic or to a primary disorder of the cerebellum.[8] MRI study has confirmed a cerebellar atrophy in POT[9] and finally transcranial magnetic stimulation (TMS), has shown POT can be reset by stimulation of the cerebellum.[10] TMS is a well-established physiological tool to understand brain function.[11] When repetitious TMS pulses are delivered to a specific target at predefined stimulation parameters, it is referred to as rTMS therapy. The fundamental mechanism of action for rTMS is modulation of brain excitability.[12] rTMS at frequencies of 5-Hz and higher has been found to transiently enhance the excitability,[13] whereas rTMS at frequencies of 1-Hz and lower has been found to depress the cortical excitability.[14] We propose a **novel approach** to investigate the clinical and physiological effects of low frequency rTMS therapy in POT. T**he overarching hypothesis** of this study is that low frequency rTMS therapy delivered to the cerebellum will modulate the cerebellar excitability and result in clinical improvements. rTMS therapy has shown positive efficacy in many neurological and psychiatric conditions.[15] rTMS therapy is FDA approved for the treatment of depression.[16] In our recent meta-analysis; we found positive outcomes with low frequency rTMS therapy in Parkinson's disease (in press). In one study of 10 patients, rTMS therapy was delivered to the cerebellum for the treatment of essential tremor in a single session. Tremors were clinically examined before and after rTMS session. The clinical improvements in tremors observed immediately after rTMS were seemed to be lost at one hour after therapy.[17] In order to determine the physiological effects related to rTMS, we will record the tremor physiology with surface electromyography (EMG). We will also record the changes in cerebellum excitability in response to rTMS using cerebello-cortical inhibition (CBI), a well-established TMS parameter.[18]

This proposal is significant because the approach is novel, innovative and promising. The findings of this study will be the first step towards development of a reliable and effective treatment for POT. In addition, the TMS related physiology will shed further insights into the pathophysiology of POT and the mechanisms underlying treatment response.

GOAL AND SPECIFIC AIMS:

The **primary goal** of this study is to test the efficacy of low frequency rTMS therapy in POT. In this one year application, we expect to enroll twenty POT patients using a double blind randomized placebo controlled crossover design. We will enroll POT patients from our large research database (IRB approved protocol 416-2002) in addition to screening outpatient clinics. We plan to obtain IRB approval over the next few months while the grant is undergoing review process. Once the study is initiated, we will collect the data over the first six months. We will then plan for data analysis and publication over the subsequent six months. We believe the pilot findings from this study will be used for development of a larger multicenter clinical trial.

The **specific aims** of the proposal are:

Aim 1: To determine the clinical impact of 1-Hz rTMS therapy in POT when delivered to the cerebellum. This impact will be evaluated by the clinical scoring of leg tremors in standing posture, and the functional assessment of gait mobility. Comparisons will be drawn between T0 (before rTMS therapy), T1 (immediately or +5 minutes after) and T2 (60+ minutes after) assessments to determine the time course of effects.
Hypothesis: 1-Hz rTMS therapy will result in clinical improvement of leg tremors and gait mobility in POT. In addition improvement in scores at T1 assessment will be greater than those recorded at T2 assessment.

Aim 2: To determine the physiological effects of 1-Hz rTMS therapy in POT when delivered to the cerebellum.
Aim 2a*:** We will determine the effects on the amplitude and frequency of tremors recorded with surface EMG. Comparisons will be drawn between T0, T1 and T2 assessments. ***Hypothesis: 1-Hz rTMS therapy will reduce the amplitude of tremors and will have no effects on the frequency of tremors. The amplitude reduction in tremors will be greater at T1 assessment than at T2 assessment.
Aim 2b*:** We will determine the effects on the cerebello-cortical inhibition measured with TMS. Comparisons will be drawn between T0, T1 and T2 assessments. ***Hypothesis: 1-Hz rTMS therapy will normalize the cerebello-cortical inhibition at T1 and T2 assessment. The effects will be greater at T1 assessment compared to that seen at T2 assessment.

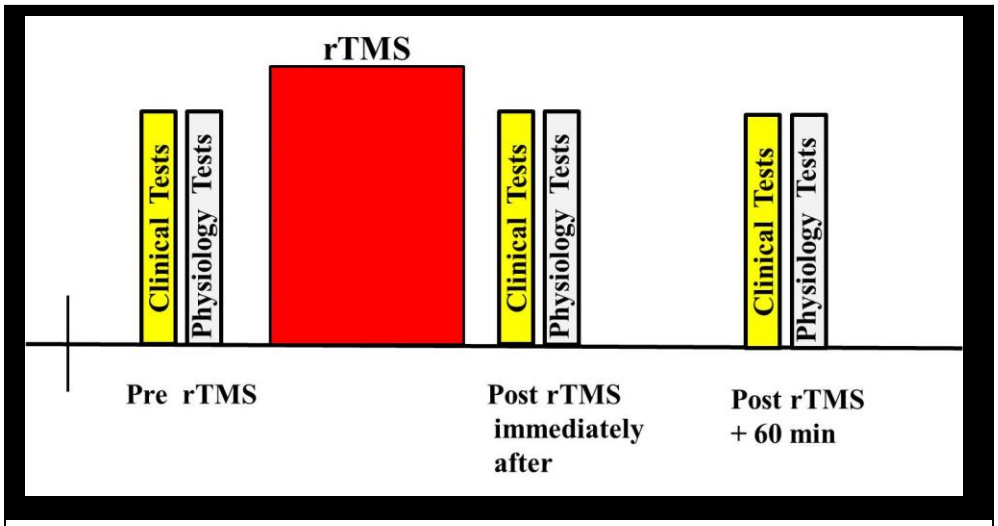

Figure 1: Clinical Tests include TRS score, leg tremor score, TUG test speed, 10m walk test time. **Physiological Tests** include amplitude and frequency of tremors, cerebello-cortical inhibition

Inclusion Criteria

- Diagnosis of primary orthostatic tremor (POT)
- Must be 30-75 years or older
- Have not responded to oral pharmacological medications for POT

- Have tolerated withdrawal of oral pharmacological medications for POT at least 12 hours prior to regular clinical visit.

Exclusion Criteria

- Must not be pregnant
- Active seizure disorder
- Significant cognitive impairment reported on history and per charts (and later confirmed with MMSE less than 24) and active psychosis per history and per patient charts
- Presence of a metallic body such as pacemaker, implants, prosthesis, artificial limb, joint, shunt, metal rods and hearing aid that is not MRI compatible

METHODS

Study design: In this application, subjects with POT will be enrolled based on clinical history, physical exam and a 13-18 Hz tremor recorded on the surface EMG in accordance with the Consensus Statement of the Movement Disorder Society.[19] In this one year study, our goal is to enroll twenty subjects (age range 30–75 years) diagnosed with POT. Potential participants will be recruited either through IRB approved database maintained by the movement disorders center or recruited by the principal investigator during an outpatient visit. Eligible individuals who are screened via the approved database (IRB #201501166) will be contacted by phone. Subjects will be off their anti-tremor medications, prior to presenting for the first visit, as standard with their clinic visit. Subjects will be explained in detail about the procedures outlined for the study and asked to provide consent. Subjects will have a detailed medical history and neurological examination using the NINDS Common Data Elements. Subjects will be randomized to receive the real and sham rTMS sessions in random order. These two sessions will be conducted on two separate days. Subjects will crossover to the other session upon completion of one session. The order of sessions will be counterbalanced across patients. Subjects will be instructed to withhold anti-tremor medications for at least 12 hours before the start of rTMS session on day 2 and will already be off anti-tremor medications during their standard clinic visit. The rationale for studying patients after overnight withdrawal from medication is that the symptoms will be maximal in this state and we want to minimize the extent that medication will affect our findings. Subjects may be followed for clinical assessment 6 months to about 2 years after the study to determine if there are residual effects of treatment. We will always make certain that patients are accompanied to the laboratory facility by a friend, relative, or spouse, or we will arrange transportation using a driving service.

Clinical assessments: All individuals in the study will be assessed using the ***Fahn-Tolosa-Marin Tremor Rating Scale (TRS)***.[20] TRS is a widely used clinical rating scale to quantify rest, postural, and action/intention tremors.[21] The scale is divided into three parts. Part A assesses examiner-reported tremor location/severity (amplitude), Part B assesses examiner-reported ability to perform specific motor tasks/functions (writing, drawing, and pouring with dominant and non-dominant hand), and Part C assesses patient-reported functional disability resulting from the tremor (speaking, eating, drinking, hygiene, dressing, writing, working, and social activities). All tremor items will be rated based on a scale of 0=none to 4=severe. Finally, the TRS includes one separate item dealing with global assessment of tremor-related disability, rated both by patient and examiner on a 5-point scale. Previous studies have shown, that the inter-rater reliability for the TRS scale using the modified Kappa statistics ranged from 0.10 to 0.65 and these reliabilities were greater for Part A items (magnitude of tremor in different body parts) than for Part B items (tremor in writing and drawings) of the TRS.[20] For outcome analysis, total tremor score and leg tremor score (derived from leg motor item on the scale) will be recorded.

Fullerton Advanced Balance Rating Scale – we will administer this assessment designed to evaluate postural instability. Lower scores are associated with greater postural stability. We will also measure the duration that the patients can maintain upright station.

Timed "Up & Go" Test (TUG) test and ***10m walk test*** will be used for assessment of functional mobility and gait speed.[22] The TUG is a mobility test that is used to measure the basic mobility skills and gait speed of people who have neurological conditions. It includes a sit-to-stand component as well as walking 3 m, turning, and returning

to the chair. People perform these tasks using regular footwear and customary walking aids. The measured outcome is the time in seconds to complete the entire sequence. The 10m walk test is another standardized test to measure gait speed. In this test, subjects are instructed to walk 10m distance and timed. The speed of walking is determined as the distance covered (10m) divided by the amount of time needed to cover the distance. The average speed of gait on a 10m test is 1.2-1.5m/sec.

Although the physician administering TMS will be aware of the status of the subject in terms of 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 assessments. Similarly, the investigators who perform 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 TMS versus sham-TMS.

Video assessment: For the outcome assessment, we will videotape the items on TRS, the TUG test and 10 m walk test. These videos will be scored by blinded rater. We will obtain consent to obtain videos of all patients. Videos of clinical exam will be scored by blinded rater before therapy (T0), immediately after (T1) and 60+ minutes after (T2) therapy in each of the rTMS sessions. Subjects will be given three options as to how they would like their videos to be used.

Physiological assessments:

Tremor electrophysiology: POT tremors will be recorded on the surface EMG for amplitude and power spectral frequency analysis. We will use Bagnoli EMG system and Trigno wireless EMG system to record the surface EMG signals arising from muscles and the accelerometer findings respectively. The muscles involved in tremors and tremor like movements will be identified in each individual for the EMG recordings. The surface electromyography (EMG) signal is a minute electrical signal that emanates from contracting muscles. Trigno wireless system has sensors that use patented parallel-bar technology. This technology guarantees high fidelity signals to be recorded. Each sensor has a multi-function design and therefore along with recording of surface EMG signal, it embeds triaxial accelerometer. The accelerometer is judiciously mounted in the sensor so that the inertial behavior of the sensor remains intuitive. Accelerometer calibration is easily performed by carefully orienting the sensor with respect to the earth's gravitational field. This process creates a selective displacement of 1 g (i.e. 9.8m/s2), which conveniently allows the software to scale the sensor outputs accordingly. Accelerometers have a range of ±1.5 or ±6 g, selectable by software. Tremor amplitude and frequencies will be calculated with the surface EMG using Bagnoli system and accelerometry recorded using Trigno system. These tremor assessments will be done at T0, T1 and T2 rTMS therapy.

Data Analysis: The EMG signal will be amplified (gain = 1000) and band pass- filtered between 20 and 450 Hz (Delsys, Boston, MA, USA) for the Bagnoli amplifier and analyzed. For analysis, the data will be digitized with 12-bit resolution by a 1401-plus (CED, Cambridge, UK) analogue-to-digital converter and digitally full-wave rectified. Sampling will be performed at 512 Hz. However, since each burst occurs at only 4-12 Hz or slower, the envelope of each burst will be the feature of interest in this study. The signals will be displayed and stored on computer disc by a software package (CED Spike 2) running on microsoft windows computer. We will use fast Fourier transform to generate auto spectra. For frequency of the tremors, the mean (± standard deviation) frequency of the 4-12-Hz range EMG spectral peak will be averaged over all muscles and over all trials recorded for each subject. The values will be estimated from the power spectra to the nearest 0.25 Hz. For amplitude of the tremors, the *y*-axis of the spectral plots will be used which represent the root-mean-square power.

TMS measure: We will record cerebellar inhibition (CBI) that is a well-established TMS measure.[23,24] A paired pulse protocol will be used with right cerebellar stimulation as the conditioning stimulus,

(cerebellar conditioning stimulus or CCS) and left motor cortex stimulation (M1) as the test stimulus (TS). We will determine the 'TS 0.5mV' which will indicate a stimulator setting (determined to the nearest 1% of the maximum stimulator output) that produces a peak-to-peak MEP amplitude of ≥0.5mV in at least five out of 10 trials. Interstimulus intervals (ISI) of 3 to 8 milliseconds at increment of 1 millisecond will be tested. Each run will consist of 10 trials of each of the paired stimuli (CCS-TS) and 10 trials of TS alone delivered in random order (70 trials in total). Inhibition trial will be expressed as a ratio of mean conditioned to mean unconditioned MEP amplitude for each subject. The intensity for cerebellar stimulation will be set at 5% of the stimulator output below the active motor threshold. Active motor threshold is the minimum intensity required to elicit MEPs of more than 50 μV above the background EMG. The cerebellar coil will be a double cone coil attached to MAGSTIM machine (Magstim Company, Dyfed, UK) positioned 3 cm lateral to the inion on the line joining the inion and the external auditory meatus. This coil position and current direction have been found to be optimal for suppressing the contralateral motor cortex. The second coil will be a flat figure-of-eight coil (70 mm mean diameter) placed on the left motor cortex. An optimal position for eliciting MEPs from the right first dorsal interosseous FDI muscle will be identified. The handle of the coil will be pointed backwards and perpendicular to the presumed direction of the central sulcus, about 45° to the midsagittal line. The direction of the induced current is from posterior to anterior, optimal to activate the motor cortex trans-synaptically. Surface EMG will be recorded from the right first dorsal interosseous (FDI) muscle with disposable silver-silver chloride disc electrodes in a tendon-belly arrangement. The signal will be filtered (band pass 2 Hz to 2.5 kHz), amplified, digitized at 5 kHz and stored on a laboratory computer for offline analysis.

RTMS THERAPY: ***Real stimulation:*** Repetitive-TMS will be <u>delivered sequentially over each cerebellar hemisphere</u>, using Neuronetics NeuroStar Transcranial Magnetic Stimulation (TMS) FDA approved TMS Therapy device. Neurostar coil 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. The current in the coil is directed downward, which will in effect induce an upward current in the cerebellar cortex. 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 interosseous 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. Similar protocol will be observed for the contralateral cerebellum. The electrical field induced by this coil is maximal beneath the center of the figure-of-eight coil.[25] Use of this type of coil stimulates a small area of the cortex of approximately 2 cm in diameter. It is presumably unlikely that the coil placed over the occiput will stimulate structures much deeper than 2 cm.[26] This means the cerebellum (at least 1.5 cm deep) will preferentially be stimulated rather than the brainstem (at least 3.0 cm deep).[26,27] The inion will be taken as a landmark of the boundary between the posterior cerebellum and the occipital cortex. We therefore will stimulate the area caudal to the inion to stimulate the posterior cerebellum.[28]

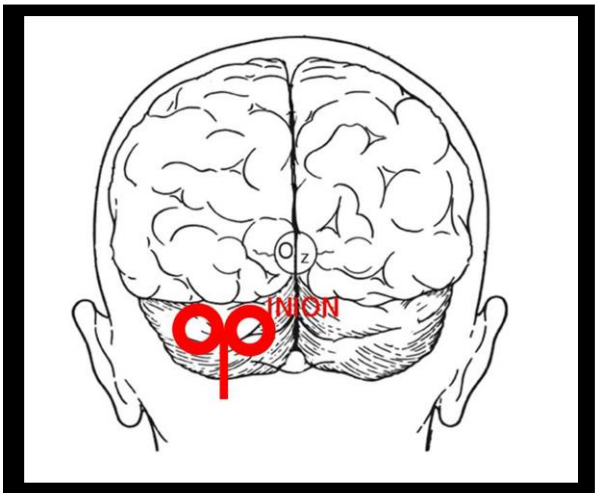

Figure 3: Figure-of-eight coil is placed 3 cm lateral to the inion on the line joining inion and external auditory meatus. The coil will then be placed on the opposite side for stimulation

Sham Stimulation: Patients randomized to receive sham treatment will undergo the same procedure for identifying stimulus location used in patients receiving real rTMS. Simulated rTMS will be administered using Magstim Placebo 70 mm figure-of-eight shaped coil which produces discharge noise and vibration similar to a real 70 mm coil without stimulating the cerebral cortex. However, in addition to obvious coil discharge noise, rTMS also causes electrical stimulation of the scalp. We will simulate this experience by attaching surface electrodes underneath the sham coil and in contact with the scalp. We will use an electromyography to administer electrical shocks to the scalp simultaneous to each simulated rTMS train. This technique has been suggested to provide more effective blinding compared to other methods use in previous controlled studies.[29]

Possible Discomfort and Risks: The main risk involved in TMS is the very rare possibility of triggering seizures. Magnetic stimulation treatment may be associated with some transient discomfort in the scalp. Typically, a twitching sensation is experienced. Some patients have complained of headache, dental and neck pain. These problems may be treated with over-the-counter medications such as Tylenol or Advil. Because of noise produced by magnetic coils, we will supply earplugs that participants may wear during magnetic stimulation treatments, in order to protect the hearing of the subjects. Repetitive TMS can have undesired side effects.[25] Guidelines for the safe use of rTMS were formulated at the 1st International Workshop on the Safety of TMS.[30] These were adopted by the International Federation for Clinical Neurophysiology and subsequently updated.[31] The proposed study will use TMS parameters well within the published safety guidelines. We will conduct careful monitoring of the participants and follow all recommended precautions for the application of TMS.

Women of childbearing age will have a urine pregnancy test to evaluate for pregnancy.

Possible Benefits: There will not be any direct benefits to the patients. This study will improve our understanding of the primary orthostatic tremor and the potential treatments.

Statistical analysis*:* The primary outcome measures in this study are change in total TRS score, leg tremor score, TUG test speed, 10m walk test time. The secondary outcome measures are amplitude and frequency of tremors on the surface EMG and the CBI recorded. Data will be presented as mean (SD) unless otherwise indicated. Each dependent measure will be examined using the following statistical approach. For each of the outcome variables, 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 within-subject factors: treatment (2 levels: active vs sham) and time (3 levels: T0, T1, and T2). If the interaction effects between stimulation arm and time are non-significant, they will be dropped. In case of significant main effects, post hoc pairwise comparisons will be corrected using Fisher least significant difference procedure in accordance with the closed test principle; i.e., post hoc comparisons will be declared non-significant if the global *p* value of the main effect (testing equality of all 2 stimulation arms simultaneously) are non-significant, but will be carried out without further correction in case of a significant global main effect. SPSS version 15.0 for Windows will be used for statistical computations. The 2-tailed significance level will be set at 0.05

The University of Florida nor the Principal Investigator hold a patent or license for any material, object or process used in this study. There is no license pending or under consideration or is there any intention to file a patent application at a later date.

Computer-based files will only be made available to personnel involved in the study through the use of access privileges, passwords and encryption. Passwords and encryption are used to ensure that the electronic data is secure and housed in a locked room.

Videos are edited in a secure research lab then the edited videos are deposited into a secured server in the University of Florida Health Science Center server. Access to the server and the videos on its restricted drive are limited to a directory group who need access to the movement disorders clinic or research videos on it

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.

Patient Stipends

Payments for mileage reimbursement will be paid to study subjects with primary orthostatic tremor. If a hotel visit is required, the study team will make the hotel arrangements for the subjects and the cost will be pre-paid.

	Screening	Day 1 visit*			Day 2 Visit 2		
		T0	T1	T2	T0	T1	T2
Screening and informed consent:	x						
History: 20min	x						
Neurological exam	x			x			x
Physical exam: 20 minutes	x						
Urine pregnancy test	x				x**		
Clinical Assessments							
Fahn-Tolosa-Marin tremor rating		x	x	x	x	x	x
Balance Scale		x		x	x		x
TUG		x	x	x	x	x	x
10 m walk		x	x	x	x	x	x
Videotape		x	x	x	x	x	x
Physiological Assessments							
Tremor recorded on EMG (Bagnoli/Trigno)		x	x	x	x	x	x
rTMS (real/sham)		x			x		
TMS recording (CBI)		x	x	x	x	x	x

* Screening can take place same day as Visit 1

**pregnancy test to be repeated if Visit 2 is more than a month later.

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