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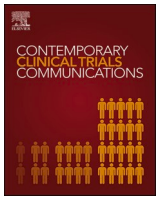

C-STIM: Protocol for a randomized, single-blind, crossover study of cerebellar repetitive transcranial magnetic stimulation (rTMS) for postural instability in people with progressive supranuclear palsy (PSP)

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ABSTRACT

Background: Methods for modulating the cerebellum with transcranial magnetic stimulation (TMS) are well established, and preliminary data from our group and others has shown evidence of transient improvements in balance after cerebellar repetitive transcranial magnetic stimulation (rTMS) in progressive supranuclear palsy (PSP). This study examines extensive posturography measures before and after 10 sessions of cerebellar rTMS and sham TMS in PSP.

Methods: Thirty subjects with PSP and postural instability will undergo cerebellar active and sham rTMS in a single-blind, crossover design with a randomized order of a 10-day intervention. Primary outcomes will be changes in sway area and medio-lateral range of sway with eyes open while standing on a stationary force-plate, and safety, tolerability, and blindedness. Secondary outcomes will include posturography and gait analysis with body-worn, triaxial inertial sensors, clinical balance scales and questionnaires, and a bedside test of vestibular function. Exploratory outcomes are changes in functional near infrared spectroscopy (fNIRS) signal over the prefrontal, supplementary motor, and primary motor cortices while standing and walking, and speech samples for future analysis.

Discussion: The C-STIM crossover intervention study adds a longer duration of stimulation and extensive posturography measures to more finely measure the improvements in balance and exploratory functional near-infrared spectroscopy (fNIRS) over the prefrontal, supplementary motor, and primary motor cortices during balance assessments before and after 10 sessions of cerebellar rTMS and 10 sessions of sham cerebellar TMS. This project will improve our understanding of the importance of the cerebellum for control of postural stability in PSP.

1. Background

Postural instability in progressive supranuclear palsy (PSP) is a significant and unsolved problem [1]. PSP is a form of parkinsonism classically characterized by early and severe balance deficits, primarily backward postural instability, leading to frequent and disabling falls. The traditional symptomatic treatments for bradykinesia and rigidity in parkinsonism (dopaminergic medication and stimulation of the basal ganglia circuitry via deep brain stimulation) are not helpful for postural instability. PSP is thus a model disorder to study interventions to improve postural instability in parkinsonian disorders.

Two preliminary studies have shown a transient improvement in balance and postural stability in people with PSP after cerebellar repetitive transcranial magnetic stimulation (rTMS) [2], but the effects of a longer duration rTMS protocol on objective metrics of postural instability and gait quality in PSP are unknown. Tau pathology in PSP is known to accumulate in the frontal motor areas, the basal ganglia, the thalamus, the midbrain and pontine regions of the brainstem, the

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dentate nucleus of the cerebellum, and in white matter tracts connecting these regions [3]. Of all these areas, the cerebellum is the most important for reflexive motor control.

We are interested in cerebellar neuromodulation for postural instability because it has been shown that the cerebellum's ability to inhibit the motor cortex is diminished in PSP and in Parkinson's disease [4–7]. Under normal physiological conditions, purkinje cells in the cerebellum normally inhibit the tonic output of the dentate nucleus to the motor cortex along the cerebello-thalamo-cortical (CTC) pathway. This inhibition is essential for corrections necessary to maintain balance and fall prevention (the so called "cerebellar-brain inhibition", or CBI). CBI is diminished in PSP and Parkinson's disease,[5 6 7] and the lack of a normal motor inhibition and error-correction response may impair rapid and fluid adjustments that are necessary to maintain balance.

Methods for modulating the cerebellum with TMS are well established [6,7], and preliminary data from our group [8] and others [9] has demonstrated transient improvements on posturography measures after cerebellar TMS in PSP. Our initial pilot data showed an improvement in posturography measures in two subjects after 10 sessions of rTMS compared to 10 sessions of sham TMS, but the outcomes were limited to only one type of posturography assessment [8]. Subsequently, a short-duration, one-session theta burst cerebellar TMS intervention in PSP recently found reduced postural sway and increased time without falls while subjects stood in tandem stance after active cerebellar rTMS compared to sham rTMS [9]. We hypothesize that multiple aspects of postural instability in PSP may benefit from repetitive sessions of high frequency cerebellar stimulation.

High frequency stimulatory cerebellar TMS is known to enhance deficient inhibitory connections along the CTC tract [6]. High frequency cerebellar TMS interventions may stimulate cerebellar Purkinje cell axons, increasing inhibition of the dentate nucleus of the cerebellum. Axons from the dentate synapse on the ventrolateral nucleus of the thalamus, influencing projections to the primary motor and premotor cortices [10].

Previous resting state functional MRI (rsfMRI) studies in PSP provide insight into changes in cortical and subcortical function after from cerebellar TMS. Whitwell et al. showed disrupted thalamocortical connectivity in PSP during rsfMRI compared to control subjects [11]. In particular, their analysis of the default mode network, basal ganglia network, and salience network in 18 PSP subjects found reduced in-phase functional connectivity between the thalamus-premotor cortex, thalamus-striatum, and thalamus-cerebellum. Several other studies have noted decreased functional connectivity in PSP between the thalamus and other cortical structures [12–15]. Others have found increased functional connectivity between cortical areas in PSP, potentially as a compensatory mechanism for known dysfunction between subcortical and cortical areas [16]. The study from Brusa et al. found increased connectivity in the bilateral caudate head rsfMRI after cerebellar TMS [6]. Taken together, the literature suggests that networks through subcortical structures, such as the cerebello-thalamo-cortical pathway, are impaired in PSP and may be influenced by cerebellar TMS interventions.

In our prior preliminary data collection, we noticed that many subjects with PSP are unable to tolerate an extensive rsfMRI protocol in our hands. We aimed to analyze rsfMRI before and after active and sham cerebellar TMS interventions, but we found excessive motion artifact resulting from the discomfort of muscular rigidity in PSP (especially midline rigidity and back pain), and from dysphagia to oral secretions resulting in coughing while lying supine in the scanner. We have also experienced issues with head coil fit related to neck rigidity and dystonia in PSP, despite attempts to pad and support the head and trial alternative head coils.

For this reason, we decided to include functional near-infrared spectroscopy (fNIRS) over the prefrontal, supplementary motor area (SMA), and primary motor cortices. A major advantage of fNIRS is that we can explore cortical activity simultaneous to balance and gait testing and mitigate the effects of motion artifact. However, fNIRS provides less spatial precision than rsfMRI and cannot specifically examine thalamic activity as it relates to the cerebello-thalamo-cortical pathway due to its limited depth sensitivity. Despite these limitations, fNIRS may still be an alternate methodology to serve as a physiological marker of motor cortical activity after cerebellar rTMS.

Based on the concept that stimulatory cerebellar TMS may help restore deficient physiological cerebellar-cortical inhibition,we hypothesize that fNIRS will show a decreased concentration of oxygenated hemoglobin in the primary motor cortex during complex motor tasks relative to a baseline motor task after active, but not sham, cerebellar rTMS. We are less certain about SMA and prefrontal fNIRS responses, but we expect an overall reduction of oxygenated hemoglobin in these areas as well because there is evidence that aging and neurodegenerative diseases increase cortical activity for balance and gait, and we may modify this abnormally increased activity with cerebellar stimulation [17]. However, recent TMS-EEG evidence suggests that prefrontal activity actually *increases* with cerebellar stimulation, attributed to an increase in the high frequency beta power [18].

This proof-of-concept C-STIM trial will examine the effect of 10 sessions of active cerebellar repetitive transcranial magnetic stimulation (rTMS) compared to 10 sessions of sham rTMS on comprehensive objective balance measures, clinical balance tests, and fNIRS over the prefrontal, SMA, and primary motor cortex in in PSP. Our crossover design will help limit other confounding clinical variables, such as cognitive and other medical comorbidity effects. We hypothesize that augmenting cerebellar inhibition via rTMS will decrease postural instability in patients with PSP by increasing normal physiological inhibition between the cerebellum and the primary motor cortex.

2. Methods

2.1. Design

This is a single-blind, crossover design trial with a 4-week TMS washout period. Neurological examination, posturography, and fNIRS will be performed 4 times: at baseline, after the 10-day rTMS and 10-day sham rTMS interventions, and after the 4-week washout. Each subject will thus have 10 active rTMS and 10 sham rTMS visits, with each session lasting approximately 20 min. The outcome assessments will be performed on the same day as the final rTMS and sham TMS sessions (within 6 h). The washout period and 10 session regimen was determined from precedent in the TMS literature [19,20].

Please see Table 1 for inclusion and exclusion criteria. An MMSE cutoff of 15 or higher is required for inclusion as per prior intervention trials in PSP, such as the 2014 davunetide trial. Subjects will not receive any new concomitant and potentially confounding courses of physical therapy during the protocol, and medications that may affect the resting motor threshold of TMS (such as stimulants) will be held constant during the study. Cholinergic, anticholinergic, dopaminergic, serotonergic sedative or NMDA receptor antagonists will be held at stable doses for the duration of the study. Coenzyme Q-10 doses will also be held at a stable dose for the duration of the study.

Demographic characterization and neurological examination will include age, gender, disease duration, PSP subtype according to the updated MDS PSP Criteria [2], and current medications. Neurological examination at baseline will include a PSP Rating Scale (PSPRS) [21] and Montreal Cognitive Assessment (MOCA) [22,23].

Subjects will be randomized to either active TMS intervention followed by sham intervention or sham intervention followed by active TMS intervention. Our initial subjects were randomized by a simple randomization function, and moving forward we will use a REDCap database randomization module, connecting the subject number with the programming code for randomization. The subjects will be blinded to the order of intervention. A blindedness questionnaire will be administered before and after the active and sham treatment blocks to

Table 1
Inclusion and Exclusion Criteria of the C-STIM study.

Inclusion Criteria
1. Probable or possible PSP by MDS PSP Criteria [2], including all subtypes with postural instability on the clinical pull test
2. Age 40–85 at the time of screening
3. Ability to stand unassisted for at least 30 s and ability to walk independently with a walker
4. Score 15 or higher on the MMSE
5. Refrain from new physical and speech therapy programs for the duration of the study
6. Remain on stable does of any cholinergic, dopaminergic, serotonergic sedative, or NMDA receptor antagonists for the duration of the study
Exclusion Criteria
1. History of cerebellar ataxia or other primary cerebellar disorder, infarcts >1cm3, >3 lacunar infarcts, space-occupying lesions (e.g. tumor), subdural hematoma, or hydrocephalus, prior diagnoses of Parkinson's disease (which has not subsequently been revised to a diagnosis of PSP) or other neurodegenerative disorders, or multiple sclerosis
2. Epilepsy, past seizure activity (not counting childhood febrile seizures), or active use of antiepileptics for seizure
3. History of head injury with a loss of consciousness for at least 15 min in the past 20 years
4. History of alcohol abuse
5. Active substance abuse
6. Prior vestibular diagnoses or previous ototoxic medication
7. Musculoskeletal disorders significantly contributing to balance
8. Sensory deficits in the feet (absent toe proprioception)
9. Any psychotic disorder or suicidal thoughts believed to represent a current safety risk, active use of antiepileptic medications, pregnancy
presence of electrically, magnetically, or mechanically activated implants or metal exposures that preclude safe TMS administration and structural MRI

assess perceived treatment (active or sham), reasons for perceived treatment, confidence in that decision, and how the treatment felt. For this proof-of-concept trial, the PI (MLD) will not be blinded to the order of intervention, in order to assist with TMS set-up using two different MagStim coils (active and sham coils) and TMS administration. The objective posturography and fNIRS outcome data will, however, be analyzed by collaborators MM, AS, and BHB in a fashion blinded to the intervention, so as to limit bias in the outcome data.

2.2. Participants and recruitment

Patients will be recruited according to inclusion and exclusion criteria listed in Table 1. Thirty participants will be recruited by neurologists in the Oregon Health Science & University (OHSU) Movement Disorders Clinic and Portland Metro neurologists. We will also recruit during local outreach and education events, and the study is searchable at clinicaltrials.gov: study #NCT04468932. The PSP diagnosis will be confirmed by the PI (MLD) at the initial screening visit.

2.3. TMS intervention

The TMS procedure will include neuronavigation with Brainsight2, using baseline structural MPRAGE MRI (see Imaging section below) fused with fiducial markers during stimulation for consistent TMS targeting (Fig. 1).

Please see our prior publication and con materials for details of methodology for neuronavigation and individualized TMS dosing, using a MagStim Rapid2 connected to an active air-cooled figure of eight flat coil (70 mm diameter) or an identical sham coil (Dale 2019), stimulating the cerebellar hemisphere ipsilateral to the dominant hand per expert consensus. For the active rTMS or sham rTMS intervention, 20 min of stimulation or sham will be performed for 10 days at approximately the same time each morning. The 4-week washout period before crossover should be sufficiently long to limit carryover TMS [19], but not so long as to be affected by the natural disease course of PSP. We will use a repetitive TMS paradigm for stimulation, because we believe the data to be more easily interpretable compared to the compressed theta burst paradigms. The rTMS will be delivered 4 s on, 8 s off at 10 Hz (100 trains and 4000 pulses total per session, each session is approximately 20 min) and 90–110% of the resting motor threshold (pending tolerability). The sham coil generates noise identical to the treatment coil delivered with identical timing to help ensure subject blinding. If the resting motor threshold is unable to be determined due to subject hand dystonia or to significant cortical atrophy, we will use the highest machine output tolerated by the subject and as allowed by the limits of cooling of the TMS stimulator.

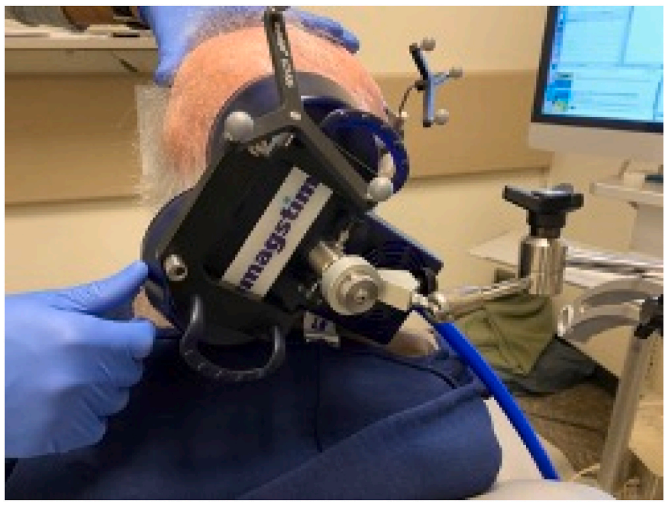

Fig. 1. Cerebellar targeting of rTMS (MagStim) with neuronavigation (Brainsight).

2.4. Primary clinical endpoints

1. Efficacy: Body sway area with eyes open while standing on a stationary force plate
2. Efficacy: Medio-lateral range of sway with eyes open while standing on a stationary force plate
3. Safety and tolerability of cerebellar rTMS in people with PSP
4. Blindedness questionnaire

2.5. Secondary clinical endpoints

1. Sensory Organization Test (Chaudry 2004) on the Neurocom Balance Master system
2. Postural Responses to backward disequilibrium from toes-up surface tilts and forward surface translations on a movable force plate
3. Instrumented aspects of the mini-BESTest scale (Franchiognoni 2010) using wearable sensors (Opals, APDM Wearable Technologies, a Clario company), focusing on postural sway in various conditions
4. Instrumented 2-min walk test with Opals obtained with MobilityLab v2 (APDM Wearable Technologies, a Clario company)
5. Activities-Specific Balance Confidence Scale (ABC) (Powell 1995) [24] from subject and care partner
6. Falls Efficacy Scale (FES-I) (Yardley 2005) [25] from subject and care partner
7. Vestibular "Bucket Test" (Zwergal 2009) [26] to monitor any changes in vestibular function

2.6. Exploratory endpoints

1. fNIRS: Relative change of oxygenated hemoglobin over prefrontal, SMA, and motor cortex during 1)standing for 60 s with eyes open compared to standing for 20 s *with the support of a walker* with eyes

open and 2)*walking with a walker* for 80 s compared to *standing quietly with a walker* for 20 s.

2. Speech samples: Because a prior cerebellar TMS study in PSP showed a signal of speech improvement [6], we will collect speech samples from participants at all 4 assessment points. We will include a recitation and a reading sample, as well as one-breath vowel production analysis. Because this is beyond the primary scope of this project, it is not discussed in detail in this paper, but remains an exploratory, yet clinically-relevant, outcome.

Primary outcomes will be body sway area and medio-lateral range of sway while subjects stand with their eyes open on a stationary force plate. Our methods using the Neurocom Smart-Equitest Clinical Research System have been detailed in prior publications [8,27]. As previously shown, the re-test learning effect for objective Neurocom measurements is minimal [28]. Safety is assured with a lightweight safety harness with sufficient slack so as to not alter the motor responses.

Secondary outcomes: Because the Neurocom Balance Master combines a force plate with a moveable platform and a moveable surround, we can deliver perturbations to assess the ability of the automatic postural control system to maintain equilibrium during external postural disturbances. Two types of balance control will be tested: 1) postural sway in quiet stance, and 2) automatic postural responses to surface perturbations. Subjects will first undergo the Sensory Organization Test of postural sway in stance [29]: The force plate will record the ground reaction forces and center of pressure (COP) for 20-s trials in 6 sensory conditions during the Sensory Organization Test (SOT): eyes open (3 repetitions), eyes closed (3 repetitions), eyes open with a shifting visual surround (sway-referenced vision, 3 repetitions), eyes open with a shifting surface (sway referenced surface, 3 repetitions), eyes closed with a shifting surface (3 repetitions), and eyes open with a shifting visual surround and a shifting surface (3 repetitions). Increased sway area represents worse postural instability, and will be reported in units of mm^2/s. During the eyes closed conditions, subjects will wear a lightweight eye mask to ensure consistent eye closure and will be tested barefoot to allow unencumbered sensory input. After the postural sway tests, subjects will be exposed to sudden perturbations of the support surface that result in backward disequilibrium [27]. Using a customized analysis protocol developed in our laboratory, we will record postural responses to backward (toes up) surface tilts and forward surface translations from CoP displacements. When standing, subjects' feet will be carefully aligned over a defined axis on the force plate, which is referenced to four vertical transducers mounted beneath a supporting center plate. For details on the custom tilt (sampling frequency, frequency of rotation) see Dale, 2017 [27].Our custom algorithm will be used to derive the total sway area and medio-lateral range of the COP, for both the SOT and the custom tilt perturbation.

Clinical tests and scales (additional secondary outcomes): These tests are more representative of challenges to balance that can be tested in clinical trials and practice. We will use wearable sensors (Opals by APDM) to instrument certain balance domains within the clinical "mini-BESTest" balance test. Subjects will wear 6 sensors: one on each foot, one on each wrist, one on the sternum, and one in the lumbar region. MobilityLab V2 software (APDM) will be used to quantify balance along with simultaneous clinical scale ratings. The mini-BESTest was derived from the "BESTest" and is a sensitive test of postural control [30]. We will perform the following tests: 1) Anticipatory postural control - sit-to-stand, rise to toes, stand on each leg independently; 2) reactive postural control - reaction to backward lean perturbations; and 3) standing postural sway - stance on flat firm surface with eyes open/-closed using templated, wide foot distance and then stance on a flat firm surface with eyes open/closed with narrow/almost touching foot position. Of these categories of the mini-BESTest, the standing postural sway tasks will be instrumented with Opals. Increased sway area accelerations represent worse postural instability, and will be reported in m^2/s^4 from the Opals data. Lastly, since the cerebellum modulates vestibular control of balance, we will also perform a simple clinical test of vestibular function in which subjects must judge the orientation of a line or subjective visual vertical called the "Bucket Test." [26] The Bucket Test, along with information from certain conditions of the sensory organization test described above, will inform us about vestibular changes related to posturography outcome data [31]. We will not collect fall diary data due to the recognized unreliability of that source of data, primarily under-reporting [32]; however, we will ask the patient and caretaker to complete the Activities-Specific Balance Confidence Scale (ABC) [24] and the Falls Efficacy Scale (FES-I) [25] to better understand if our TMS intervention translates to clinically meaningful balance improvements. Though it is not as sensitive to balance changes as our mobile sensor data, the PSP Rating Scale [21] will be collected for comparison to the current clinical gold standard.

2.7. Exploratory FNIRS outcome

A continuous wave portable fNIRS system (Artinis Medical Systems) will be used to record cortical activity at 50Hz for the standing and walking trials described above. A neoprene head-cap (fiber holder) marked with labels of the international 10–20 electroencephalography system and predetermined locations for the optodes will be placed on the participant's head (Fig. 2). See supplemental materials for additional fNIRS methodology details.

2.8. Sample size

We plan to enroll a total of 30 subjects to provide 80% power for us to detect a 50% difference (0.50 effect size) in sway area and medio-lateral sway range when comparing sway in the active rTMS condition to the sham condition, assuming 2-sided hypothesis testing and an alpha level of 0.05. This effect size is based on our published preliminary data [8]. We expect this result to be a clinically meaningful effect size because a recent study in our laboratory found a significant, but smaller, effect size of 0.25 on the same measures of postural sway after a rehabilitation intervention in people with Parkinson's [33], and the 0.25 effect size related to subjects' perceived improvement in balance. This study will confirm effect sizes for potential outcome measures for a future and larger randomized clinical trial of rTMS for postural instability in PSP.

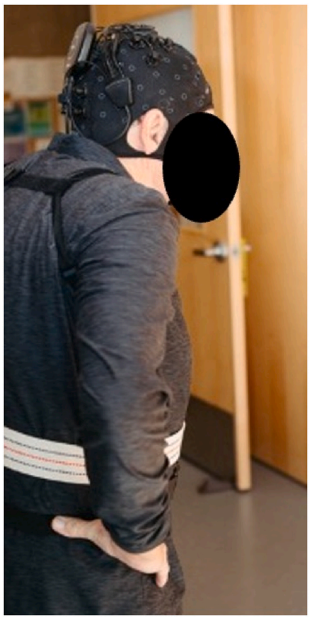

Fig. 2. fNIRS with full head cap (Artinis).

2.9. Data analysis plan

Prior to formal hypothesis testing, descriptive statistics will be used to characterize the study population at various study time points (i.e., before and after the sham and active rTMS sessions). The analyses will then rely on the use of linear mixed effects (LME) models, which are ideal for crossover designs for several reasons, including the fact that they: 1) allow for direct testing of the treatment effect, as well as potential sequence or carry-over effects, 2) account for the fact that the repeated observations on individual subjects are correlated over time, and 3) may include relevant covariates [34]. *Primary Outcome:* Based on our preliminary data, we will quantify the change in sway area and medio-lateral sway range, indicative of postural balance after either sham or active rTMS intervention compared to baseline. We will also compare the sway metrics after sham intervention to the baseline sway values as an additional check for sham study effects. As previously shown, objective Neurocom measurements show minimal re-test learning effects [28]. We will then test for a difference between intervention effects using linear mixed models. Independent variables in the LME model will include treatment group, time, group × time interaction, and sequence order. Random subject effects will be used to account for within-subject correlation. Prior to testing for treatment effects, the LME will allow us to test for the presence of any meaningful carry-over or sequence effects. Residual diagnostics will be performed and if a parametric approach is deemed inadequate, a non-parametric approach relying on Wilcoxon signed rank tests will be utilized for individually testing similar hypotheses as in the LME. All analyses will be conducted in collaboration with the biostatistician (BHB) using SAS v9.4 or STATA 16.

2.10. Potential problems

1. *Depth of Stimulation and Ability to Influence Connectivity*: Generalized atrophy in this patient population increases the distance from the scalp surface to the cerebellum; however, our published preliminary data indicates that we are able still to target the cerebellum with sufficient depth. We can use measurements of scalp to cerebellar cortex distance from BrainRuler software for posthoc regression of depth of stimulation [35].
2. *The effects of TMS stimulation may also depend on the relative anatomical integrity of the CTC pathways:*

In addition to classic midbrain pathology in PSP, it is well established that tau pathology is prominent in the white matter, and this may affect neural transmission along CTC pathways. We include FLAIR sequences along with our structural baseline images, so white matter burden will be assessed in a post-hoc analysis if needed.

3. *Potential Carryover Effects:* A crossover design always has the potential for misleading carryover effects between interventions. We have included a washout period between sham and active TMS as used in previous TMS crossover studies [19], and we will check our assumption of negligible carryover effects. Carryover of the active TMS intervention will in and of itself be important for ascertaining the potential duration of treatment effect.
4. *Tolerability of Balance Testing:* Based on our preliminary data, we do not anticipate problems with subjects tolerating the force plate platform testing in a harness. However, even with a gait belt for safety, subjects may not be able to complete all portions of the mobile sensor balance testing (for example, standing on one leg). Any improvement on aspects of balance would be notable for this population, however.

3. Discussion

C-STIM is the first study to examine detailed posturography and gait outcomes in PSP after active cerebellar and sham rTMS in a crossover design and the first to apply 10 days (instead of 1 day) of treatment. This crossover protocol provides an important opportunity to examine the clinical effects of cerebellar TMS in PSP without cognitive, medication, or other significant between-group confounders. Minimizing confounders is especially important for trials in relatively rare diseases such as PSP, which tend to have lower subject and group numbers. It is also the first study to examine fNIRS outcomes simultaneous to balance testing before and after TMS.

We expect to find reduced postural sway after active compared to sham cerebellar rTMS. Based on our own and prior studies we hypothesize that stimulatory 10Hz cerebellar rTMS will help restore deficient cerebellar-brain inhibtion in PSP, and we thus expect reduced primary motor cortical activity on fNIRS after active but not sham stimulation. This study will determine effect sizes for potential outcome measures for a future and larger double-blind randomized clinical trial of rTMS for postural instability in PSP.

In future studies, the cerebellar TMS intervention could also be paired with physical therapy interventions to enhance neuroplasticity and safety for balance rehabilitation. TMS paired with rehabilitation is under investigation for multiple neurological conditions including upper extremity ischemic stroke [36] and gait impairment in Parkinson's disease [37], with the rationale that priming the brain prior to rehabilitation exercises will promote neuroplasticity and increase the efficacy of rehabilitation.

C-STIM focuses on postural instability in PSP, but TMS paired with rehabilitation may also provide benefit for refractory postural instability in advanced Parkinson's disease. Currently available pharmacological and DBS interventions for bradykinesia and rigidity have limited benefit for backward postural instability or frequent falls in people with idiopathic PD, especially in later stages [38–40]. Severe backward falls and weak postural responses occur early in the disease course of PSP and later in advanced PD [41]. Difficulty with postural transitions for rising from a chair and turning due to weak anticipatory postural adjustments also occur earlier in PSP than in PD. Cerebellar inhibition of the motor cortex is diminished in advanced PD, similar to PSP [5]. Though the underlying protein pathology is different, the affected neural circuitry for severe postural instability in PSP and Parkinson's disease is likely to be the same.

Cerebellar TMS could thus be used as an add-on therapy for postural instability in PSP and in advanced Parkinson's disease, or as part of a proactive physical therapy program. Because severe falls often occur in PSP early in the disease course, PSP is a model disorder to study early interventions to improve balance and postural instability in parkinsonian disorders. Compared to PD, in PSP the effect of cerebellar neuromodulation will be seen within a smaller sample because subjects can be tested earlier in the disease course when they have fewer confounding symptoms of advanced disease (i.e., severe bradykinesia). As a proof-of-concept study, the C-STIM trial probes networks relevant for postural instability and has the potential for wide applications in neurodegenerative diseases.

4. Ethics and dissemination

The protocol has been approved by OHSU's IRB (STUDY00020341). All participants will provide written informed consent and will be free to withdraw from the study at any point without adverse effects on their clinical care. The current standard of care in PSP includes frequent courses of gait and balance-focused physical therapy (PT), along with a consistent home exercise program. We acknowledge the tremendous importance of exercise and physical therapy in PSP. For this reason, we will encourage participants to continue their baseline exercise programs and they may continue any active PT programs during the study. For data integrity, they may not begin NEW or altered physical therapy or exercise programs.

All adverse events will be recorded in a REDCap database. Serious

adverse events will be reported whether they are determined to be related to the intervention or unexpected. Fall prevention will be paramount. To limit subject fatigue and fall risk, we will transport subjects in a wheelchair to and from their vehicle/parking areas as well as while navigating the research facility. The study team and MR technicians are trained in safe PSP patient handling and postural instability testing. Subjects will wear a lightweight gait belt without metal parts. Safety during force plate testing will be assured with a lightweight safety harness with sufficient slack so as to not alter the motor responses. Research assistants will be present in the MR suite to assist the MR technician with patient transfer in and out of the scanner. For TMS and MR safety, subjects at risk of seizures or with electrically, magnetically, or mechanically activated implants or metal exposures will be excluded from the study (see Table 1). Seizure risk will be minimized by following published TMS paradigm safety tables, including a minimum 2:1 ratio of "off" vs "on" stimulation time. Earplugs for all participants and study personnel will be mandatory to assure hearing protection.

Study results will be presented at national and international neurology and brain stimulation meetings and published in neurology or neuromodulation-focused journals regardless of whether they are positive, negative, or inconclusive. Final study results will also be published on clinicaltrials.gov.

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Authors' contributions

MLD: conceived of the study design, obtained funding, assisted with pilot data collection, drafted the manuscript.

MM: designed the posturography and fNIRS measures, performed preliminary posturography analyses, reviewed the manuscript.

AS: assisted with pilot MRI data collection and performed MRI analysis, reviewed the manuscript.

BHB: assisted with data analysis and randomization plans, reviewed the manuscript.

AP: assisted with pilot data collection, reviewed the manuscript.

GH: assisted with pilot data collection, reviewed the manuscript.

CSB: assisted with pilot data collection, reviewed the manuscript.

AR: assisted with pilot data collection, reviewed the manuscript.

RLF: provided TMS equipment, assisted with technical aspects of TMS, reviewed the manuscript.

JFQ: assisted with study design, reviewed the manuscript.

FBH: assisted with study design, reviewed the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

OHSU and F.B. Horak have a significant financial interest in APDM Wearable Technologies (A Clario Company), a company that may have a commercial interest in the results of this research and technology. This potential conflict has been reviewed an managed by Oregon Health & Sciences University.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101165.

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