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# Cerebellar rTMS for motor control in progressive supranuclear palsy

*Keywords:*
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Speech

A B S T R A C T

*Background:* Stimulatory cerebellar TMS is a promising tool to improve motor control in neurodegenerative disorders.

Objective/hypothesis: Our goal was to use 10Hz cerebellar rTMS to augment cerebellar-brain inhibition (CBI) for improved postural stability and speech in patients with progressive supranuclear palsy (PSP).

*Methods:* We performed CBI assessments with neuronavigation before and after high frequency cerebellar rTMS or sham TMS in two patients with PSP, using a double cone coil for the conditioning pulse and a figure-of-eight coil for the test pulse and treatments. We collected posturography data and speech samples before and after treatment.

*Results:* After treatment, CBI increased by 50% in subject 1 and by 32% in subject 2, and postural stability and speech improved. The protocol was well tolerated, but the sham was not consistently believable.

*Conclusion:* Cerebellar rTMS may improve postural stability and speech in PSP, but cooled coils with vibrotactile sham capability are needed for larger future studies.



*Dear Editor*

Cerebellar TMS is a promising therapeutic tool to improve motor control in ataxia, parkinsonism, and stroke [1–3]. It is believed that high frequency stimulation of the cerebellum in neurodegenerative disorders may restore the normal, physiological inhibition that the cerebellum exerts on the motor cortex for motor control (cerebellar brain inhibition, or "CBI"). The proposed mechanism of CBI restoration via cerebellar stimulation is that increased Purkinje cell output reduces the tonic dentato-thalamo-cortical faciliatory drive via engagement of the cerebello-thalamo-cortical pathway [4]. Because inhibition is essential for motor control, restored CBI may improve both voluntary and reflexive movements.

Here, we explored CBI techniques and repetitive cerebellar stimulation with sham for postural instability in two patients with progressive supranuclear palsy (PSP). PSP is a neurodegenerative disorder with prominent motor dysfunction, including dysarthria and impaired postural stability [5]. Severe backward falls occur early in the disease course, and there are no effective treatments for postural instability and backward falls in PSP beyond physical therapy. Tau pathology in PSP accumulates in the dentate nucleus of the cerebellum and in related white matter tracts [6]. Others have shown that CBI is diminished in PSP and in Parkinson's disease [7–9]. We hypothesized that augmenting CBI in PSP would improve speech and postural stability when measured with objective posturography.

## 1. CBI

Prior to CBI testing, resting motor thresholds with specific machine outputs were obtained from all 3 calibrated coils (70mm figure-of-8 with Magstim Bistim2 for the test pulse, 110mm double cone with Magstim Bistim2 for the cerebellar conditioning pulse, and 70mm air-cooled figure-of-8 coil with MagStim Rapid2 for rTMS treatment). We used Brainsight2 with the subjects' own images for consistent cerebellar and M1 targeting. The bistim was uncoupled and connected to a digitimer to deliver pulses at 90% RMT at 0, 3, 5, 8, 10, 12, and 15 m.

### 1.1. Repetitive cerebellar stimulation

During extended cerebellar rTMS treatments the patient leaned forward on a firm wedge with his head turned to the right. We chose repetitive rather than theta burst stimulation to limit intra-individual variability within this paired-pulse paradigm. 4,000 pulses were delivered with a 70mm figure-of-8 coil at 10 Hz (4 seconds on, 8 seconds off, 100 trains, machine output 90–110% of RMT, pending tolerability). Subjects underwent 10 days of active treatment and 10 days of sham treatment, separated by a month.

### 1.2. A note on coils for paired-pulse and repetitive cerebellar stimulation

A different cone was used for the conditioning pulse of the CBI portion of our protocol and the cerebellar repetitive treatments. We did not have a double cone coil with air cooling capabilities that was capable of lasting the duration of a treatment session without overheating. Hardwick et al. showed that double cone coils are necessary for CBI protocols [10], but cooled double cone coils for high-output repetitive treatments are not readily available commercially. To ensure consistency of MEP results, we measured

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the baseline RMT with each coil paired with its associated stimulator (BiStim for the double cone and Rapd2 for the figure-of-8). Augmenting CBI was feasible in our population using an air-cooled figure-of-eight coil for repetitive stimulation and a double cone coil for the cerebellar conditioning pulse. Compared to other populations, the increase in CBI may be relatively easy to obtain in PSP patients with known diminished CBI and relatively excitable motor cortices at baseline [7].

## 2. Sham cerebellar stimulation

A mu-metal insert and a spacer was attached to the figure-of-eight treatment coil and the coil was placed flush to the cerebellum as in the active condition, keeping sound and stimulation parameters equal to those in the active condition. For subject 1, in an effort to augment the tactile stimulus of the sham, we added superficial electrical stimulation with alternating current in pulses that matched the TMS parameters, delivered by one flat electrode just under the hairline near the right cerebellum and one electrode more laterally over the trapezius muscle at the same level of the neck. A similar electrical sham method has been used by our lab in the frontalis region for addiction studies [11]. For subject 2 we used a magnetic-blocking spacer only without superficial electrical stimulation.

### *2.1. A note on sham methods for cerebellar stimulation*

Current approaches for sham cerebellar stimulation include adding spacers with magnetic-blocking mu-metal to the treatment coil, turning the angle of the coil to avoid stimulation of the target, and stimulating above and below the target. To achieve a relatively thin and cooled treatment coil that would fit over the lateral cerebellum without encroaching on the subject's shoulder, we created our own sham with magnetic blocking mu-metal attached to our relatively thin, air-cooled figure-of-8 coil. This coil is thinner than currently available figure-of-8 coils with both cooling and placebo capabilities. With the addition of the electrical sham over the paraspinal region we noted an unexpected inhibition of the MEP and elected to leave the electrical stimulation off for our second subject in this pilot study. Further, we became concerned that the superficial electrical stimulation may have unknown effects on the vestibular system. Finally, the burning sensation produced by the superficial electrical stimulation was not a convincing replication of the tactile pressure over the paraspinal region produced by the active TMS treatment. The burning sensation did not reasonably mimic the vibro-mechanical pressure of active stimulation in the posterior head and neck region, and we could not replicate masseter twitching, even when moving the second electrode over the masseter region. The subject was able to guess the sham in this condition. In sham condition 2 with a magnetic-blocking spacer only, without superficial electrical stimulation, the subject was unable to guess the sham condition.

## 3. Tolerability of the TMS protocol

Both subjects tolerated the protocol. We did not observe reflexive neck extension with the cerebellar treatments, perhaps because pre-existing neck rigidity in PSP precludes reflexive neck extension. Jaw twitching (masseter muscle contraction from the cerebellar stimulation) was noted in both subjects during the active condition only, but subjects did not complain about or comment on this. Both subjects complained of mild neck pain after treatment sessions due to right rotation of the neck (alleviated by raising the wedge and adding pillows in subsequent treatment sessions).

## 4. Posturography

Subjects stood with eyes open on a firm platform referenced to four vertical force transducers (Neurocom International, Inc, Clackamas, Or), and vertical forces were used to calculate changes in the center of pressure (CoP) at 100Hz sampling frequency.

## 5. Speech

Subjects read a standard passage before and after active and sham stimulation. Physical and speech therapy were suspended for the duration of the study.

## 6. Results

After treatment, the average motor evoked potential decreased from 1.41 to 0.71 at the 5 m cerebellar-M1 interstimulus interval, representing a 50% augmentation of CBI in subject 1. As mentioned above, we found unexpected inhibition with the superficial electrical sham in subject 1. In subject 2, with the same parameters, but no superficial electrical stimulation, the average motor evoked potential decreased from 1.45 to 0.99 at the 5 m interstimulus interval, representing a 32% augmentation of CBI. In this case there was no inhibition with the sham (Table 1). The data suggests that subjects' backward stability improved when standing on a force plate, as evidenced by reduction of the backward center of pressure excursion (less sway in the posterior direction, see Fig. 1 for example CoP excursion tracings). Subject 1 appears to have some improvement in postural stability with the sham as well, possibly due to the unexpected inhibition we noted in this condition. Quality of speech when reading a standard passage also improved after cerebellar stimulation; in particular we noted improvements in halting speech, articulatory struggle, article misuse, and phonemic phonological errors. Table 2 shows phonemic and article errors decreased in subject 1 and pace of speech improved in subject 2. See supplementary audio for speech recordings pre- and post-treatment, at washout, and after sham. The most apparent change was in pace in subject 2 from baseline to after cerebellar treatment (time to read 4 sentences decreased from 60 to 44 seconds). The data taken together do not suggest that practice effects are responsible for this change.

**Table 1**
MEP changes before and after active and sham repetitive cerebellar stimulation
At intermediate interstimulus intervals (5 m and 8 m) the size of the MEP decreased after active stimulation (negative % Δ pre/post values), indicating cerebellar-brain inhibition. The sham treatment with superficial electrical stimulation also induced inhibition in subject 1, but in subject 2 the sham without superficial electrical stimulation did not result in MEP inhibition.

| | 0 m | 3 m | 5 m | 8 m | 10 m |
|---|---|---|---|---|---|
| Subject 1 | | | | | |
| baseline | 1.54 | [a] | 1.41 | 1.4 | 0.91 |
| post active | 1.33 | 0.68 | 0.71 | 1.02 | 0.62 |
| % Δ pre/post active | −13.39 | [a] | −49.6 | −26.88 | −32.2 |
| washout | 1.48 | 2.48 | 1.81 | 1.78 | 0.68 |
| post sham | 0.88 | 0.69 | 0.68 | 0.46 | 0.55 |
| % Δ pre/post sham | −40.56 | −72.16 | −62.56 | −74 | −19.22 |
| Subject 2 | | | | | |
| baseline | 1.68 | 1.7 | 1.45 | 1.36 | 1.47 |
| post active | 1.03 | 1.02 | 0.99 | 1.2 | 1.14 |
| % Δ pre/post active | −38.63 | −39.89 | −32 | −12.05 | −22.53 |
| washout | 0.53 | 0.34 | 0.49 | 0.26 | 0.3 |
| post sham | 0.41 | 0.64 | 0.84 | 0.82 | 0.78 |
| % Δ pre/post sham | −23 | 89.83 | 70.78 | 212.05 | 157.12 |

[a] Data not collected.

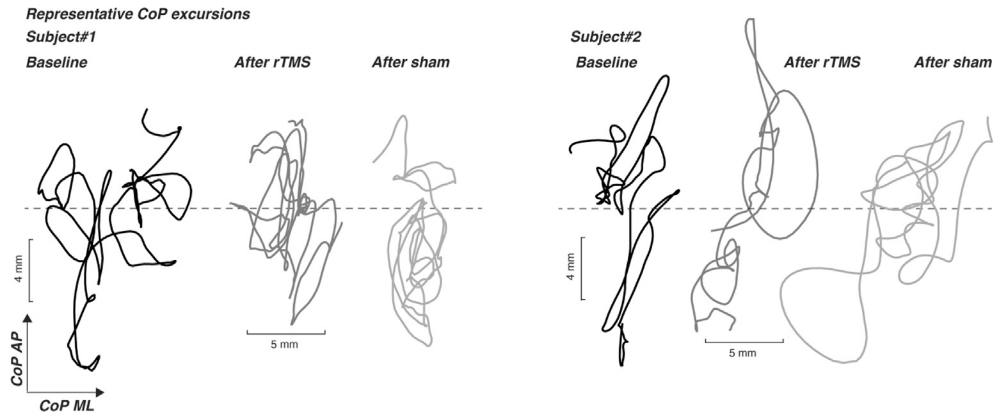


**Fig. 1.** Representative center of pressure excursionsCoP
AP: center of pressure anterior-posterior; CoP ML: center of pressure medio-lateral
Tracings represent body center of pressure shifts (sway trajectory) with the patient standing quietly on a firm, stationary platform with eyes open. Compared to baseline, both subjects showed a tendency for less *backward* center of pressure excursion after active cerebellar TMS (seen in the figure as less sway trajectory below the dotted line), and a more even anterior-posterior center of pressure balance. Subject 1 additionally demonstrated less medio-lateral sway after active cerebellar TMS, though this subject appeared to have some improvements overall after the sham treatment, as well (please see our interpretation in the text).

**Table 2**
Speech when reading a portion of the "Rainbow Passage."
Subjects were instructed to read a standard passage (the "Rainbow Passage") before and after 10 active and 10 sham cerebellar TMS treatments. With active cerebellar rTMS compared to sham, subject 1 displayed less errors (phonemic and article substitutions). Phonemic phonological errors consist of sound substitutions, for example "from" instead of form. Article errors involve words such as *a* or *the*. Subject 2 displayed less errors and a reduced total time for passage recitation, suggestive of improved halting speech or improved articulatory struggle with active cerebellar rTMS. Please see supplementary audio files.

| | Time (s) | # phonemic errors | # article substitutions, deletions, or additions | Total # of errors |
|---|---|---|---|---|
| Subject 1 baseline | 41.52 | 2 | 4 | 6 |
| Subject 1 post-treatment | 37.36 | 0 | 1 | 1 |
| Subject 1 washout | 33.36 | 1 | 3 | 4 |
| Subject 1 post-sham | 33.24 | 0 | 3 | 3 |
| Subject 2 baseline | 60.04 | 0 | 4 | 4 |
| Subject 2 post-treatment | 44.27 | 0 | 1 | 1 |
| Subject 2 washout | 59.73 | 1 | 3 | 4 |
| Subject 2 post-sham | 60.10 | 1 | 1 | 2 |

This small study suggests that cerebellar rTMS with neuronavigation may result in improved postural stability and improved speech in PSP, though certainly larger studies are required. Any improvement in symptoms in PSP is notable given the lack of currently available therapies for this relentless disorder. We hypothesize that the mechanism of action is engagement of the cerebello-thalamo-cortical pathway for motor control. Larger studies are needed to confirm this finding. Objective voice analysis is needed to quantify speech changes in PSP after cerebellar stimulation (for example, utterance length and prosody). Future studies of balance changes in PSP after cerebellar stimulation may include postural response to platform tilts and translation. Cerebellar TMS could be pursued in moderately advanced Parkinson's disease as well, because postural reactions are a symptom of advancing Parkinson's disease that is often refractory to other standard treatments such as dopaminergic therapies and current VIM/STN targets for deep brain stimulation.

Cerebellar TMS to modulate the cerebello-thalamo-cortical pathway may be used as a proof-of concept intervention for more durable cerebellar neuromodulation interventions, however, commercially-available cooled coils with vibrotactile sham capability to replicate masseter twitching are needed for future studies. Careful cerebellar TMS trials with attention to sham will advance cerebellar neuromodulation treatments in neurodegenerative diseases.

## Conflicts of interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

## Ethics in publishing

Informed consent was obtained from all subjects (MUSC Institutional Review Board Pro00076691).

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## Appendix A. Supplementary data

Subjects were instructed to read a standard passage (the "Rainbow Passage") before and after 10 active and 10 sham cerebellar TMS treatments. Subjects held the text at a comfortable distance from their eyes and used reading glasses if needed.Text of Rainbow Passage "When the sunlight strikes raindrops in the air, they act as a prism and form a rainbow. The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds it..."The Rainbow Passage, a public-domain text, can be found on page 127 of the 2nd edition of Grant Fairbanks' Voice and Articulation Drillbook. New York: Harper & Row.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.07.017.

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