Brain Stimulation 12 (2019) 1581–1582

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

High frequency repetitive transcranial magnetic stimulation for primary progressive apraxia of speech: A case series☆

Keywords:
Transcranial magnetic stimulation
Apraxia of speech
Neurodegenerative disease

Dear Editor

Apraxia of speech (AOS) is a disabling speech disorder which affects the programming of motor speech production, resulting in the inaccurate production of sounds. The speech difficulties produced by AOS can limit a patient's ability to communicate, significantly affecting quality of life. Primary progressive apraxia of speech (PPAOS) is AOS presenting as the first or only symptom of a neurodegenerative condition. The mainstay of treatment in PPAOS is speech therapy; however, efficacy is limited especially as the disease progresses [1]. High frequency repetitive transcranial magnetic stimulation (rTMS) is a neuromodulation technique which uses magnetic energy to increase neuronal excitation in specific brain areas. It has been used to improve language function in patients with neurodegenerative speech and language disorders, including in one case report, PPAOS [2–5]. However, the role of rTMS in PPAOS has not been systematically studied.

In this case series, 4 participants with PPAOS underwent 10 sessions of high frequency rTMS targeting the left (dominant) dorsolateral prefrontal cortex (LDLPFC) over a 4-week period. All participants were right-handed and native English speakers. The LDLPFC was chosen based on a case report in which high frequency rTMS was associated with improved outcome in a participant with PPAOS [5], and further supported by a recent functional imaging study demonstrating reduced connectivity between the LDLPFC and other language regions in patients with this condition [6]. rTMS was delivered using a 75mm figure-of-eight coil and the Magpro X100 stimulator (MagVenture Corporation, Farum, Denmark). The University of Miami Institutional Review Board approved the study, and all participants provided written informed consent. Prior to rTMS, participants were screened for safety against known exclusion criteria [7]. Participants were encouraged to continue speech therapy while enrolled in the study.

During each session, 2,000 pulses (50 trains, 28-s inter-train interval, total 24 minutes) were delivered at 90% of the resting motor threshold to the LDLPFC. These parameters were based on prior reports [2,5] and were consistent with accepted safety guidelines [7]. The LDLPFC was identified using a procedure described elsewhere [8]. The primary outcome was change in speech quality post-rTMS as measured by the Apraxia of Speech Rating Scale (ASRS) [9] assessed by a blinded speech-language pathologist. To maintain blinding, participants were videoed performing the same speaking tasks (taken from the Apraxia Battery for Adults, second edition) [10] before and within one week after completing the rTMS protocol; the rater evaluated the videos in random order after the study had concluded. Secondary outcomes included a comparison of composite scores from the Boston Diagnostic Aphasia Examination (BDAE) and the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency subtest, and participant self-reported improvement on a Patient Global Impression of Change (PGIC) scale.

All participants (2 males, 2 females; mean age 76.5, range 64–85) carried a diagnosis of primary progressive apraxia of speech, and reported a disease duration of 4 years at the time of entering the study. Two participants, both female, were later diagnosed with corticobasal syndrome, and one male participant (002) was diagnosed with dementia (unknown type). Of note, the latter patient underwent only 9 sessions of rTMS due to an episode of presyncope and hypotension prior to one of the planned sessions. No adverse effects were reported.

Baseline ASRS scores ranged from 14 to 54 (mean 32.75 ± 16.52 points), and baseline AOS severity scores (from the ASRS) ranged from 1 to 4 (mean 2.50 ± 1.29 points). Overall, 3 of the 4 participants showed improvement in both total ASRS score (mean improvement 8.75 ± 8.06 points) and AOS severity score (mean improvement 0.75 ± 0.50 points; each of the 3 who improved decreased their score by 1 point) post-rTMS. Of the participants who showed improvement, two self-reported improvement in speech on the PGIC scale; the third self-reported improvement overall, but did not note a change in speech. The participant who did not show objective improvement did self-report improvement in speech. There were no significant changes seen on performance of the BDAE or D-KEFS Verbal Fluency subtest. Results are summarized in Table 1.

To our knowledge, this is the first reported case series of participants undergoing high frequency rTMS for PPAOS. The results showed modest benefit of rTMS in 3 out of 4 participants, as measured by improvement in ASRS scores and the AOS severity scores. Of note, the participant who did not show improvement also had evidence of cognitive dysfunction at baseline (and carried

☆ Prior presentations at meetings: Results from this project were previously presented at the American Academy of Neurology annual meetings (2018, 2019) in the form of poster presentations.

https://doi.org/10.1016/j.brs.2019.07.007

Table 1
Results

Participant ID	Gender	Age (years)	Disease Duration (years)	Baseline MMSE,/30	Baseline ASRS Total Score,/64	Post-rTMS ASRS Total Score,/64	Baseline ASRS AOS Severity Score,/4	Post-rTMS ASRS AOS Severity Score,/4	Change in BDAE, Composite z Score	Change in D-KEFS Fluency, Composite z Score	PGIC Overall Score	PGIC Speech Score
001	Female	64	4	27	34	26	3	2	−0.32	−0.58	1	4
002	Male	78	4	20	14	16	1	1	0.01	−0.75	4	2
003	Male	85	4	27	29	17	2	1	0.36	0.08	4	2
004	Female	79	4	28	54	37	4	3	1.14	0	5	1

*Key: AOS, apraxia of speech; ASRS, Apraxia of Speech Rating Scale; BDAE, Boston Diagnostic Aphasia Examination; D-KEFS, Delis-Kaplan Executive Function System; MMSE, Mini Mental State Examination; PGIC, Patient Global Impression of Change; rTMS, repetitive transcranial magnetic stimulation.

a diagnosis of dementia, unknown type) which may have interfered with his ability to fully participate in all of the speaking tasks and influenced his performance.

Participants did not show consistency in self-recognition of their speech changes. Of the 3 participants who showed improvement on the primary outcome measure, only 2 self-reported improvement in speech on the PGIC scale. The participant who did not show improvement on the objective outcome measures did report improvement. While it is difficult to draw definitive conclusions with a small sample size, this suggests that perhaps the changes seen over the brief course of the study were too small to be clinically meaningful, at least for some participants.

This series was limited by the small size, and was inadequately powered to detect a statistically significant change in the primary outcome measure. It also lacked a sham control, though our primary outcome was assessed using a blinded rater. As participants were encouraged to continue speech therapy during the study, it is also difficult to assess the role of speech therapy in the participants' improvement. Future studies comparing speech therapy alone vs. speech therapy plus rTMS may be helpful in elucidating the contribution of rTMS to the improvement observed. Finally, though 3 out of 4 participants showed improvement at follow-up within 1 week of completing the rTMS protocol, it remains unclear how long the benefits will persist.

In summary, this small series demonstrates that high frequency rTMS may have a potential role as an adjunct therapy for PPAOS. More studies are needed to determine the best stimulation parameters, optimal targets, and long-term effects of rTMS in this population.

Declarations of interest

None.

Acknowledgments

The authors wish to thank the study participants and their families for their participation in the study. This work was supported in part by a grant from the Parkinson's Foundation.

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2 July 2019
Available online 13 July 2019