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Transcranial Magnetic Stimulation Does Not Improve Mild Cognitive Impairment in Parkinson's Disease

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Keywords

Parkinson's disease; Mild Cognitive Impairment; Repetitive Transcranial Magnetic Stimulation; Randomized Controlled Trial

Current treatments minimally impact Parkinson's disease's (PD) cognitive decline (1). Repetitive transcranial magnetic stimulation (rTMS) is a potential therapy for PD mild cognitive impairment (PD-MCI) that can improve cognitive functioning in healthy older adults and PD patients with normal cognition (2). The dorsolateral prefrontal cortex (DLPFC) is a key node in cognitive networks affected by PD (3) and is a common therapeutic target for neuromodulation. We thus studied the potential benefits of bilateral DLPFC 20 Hz rTMS for two weeks in a randomized sham-controlled clinical trial in 46 PD-MCI patients (real: 22, sham: 24; see supplementary material for Consolidated Standards of Reporting Trials (CONSORT) figure, Clinical and Demographic Characteristics and detailed Methods).

No significant group difference was found for our primary outcome: change from baseline to post-TMS on the total score of the Dementia Rating Scale-2 (DRS-2) (4) (Table 1). There was no significant difference between groups on the Clinical Global Impression of Improvement ($\chi 2$, $p = 0.83$) with 45% of rTMS and 58% of sham-treated participants

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The authors have no conflicts of interest to disclose.

Authors' Roles: I. Buard conducted the study, reviewed and revised the manuscript; D.M. Sciacca drafted and reviewed the manuscript; C.S. Martin conducted the study and reviewed the manuscript; S.H. Sillau performed the statistical analyses; S. Rogers conducted the study; M.R. Greher reviewed the manuscript and assisted with study design; R. Chen revised the manuscript and assisted with study design; B.M. Kluger conceptualized the study, conducted the study, reviewed and revised the manuscript. All authors have reviewed the final version of the manuscript.

reporting at least minimal improvement, and 23% of rTMS and 29% of sham-treated participants reporting “much” or “very much” improvement. Regarding secondary outcomes, there was a significant group difference on the initiation/perseveration subscore of the DRS-2 and the Symbol Digit Modalities Test (SDMT) favoring the sham group. While there were no other significant group differences, the real rTMS group significantly worsened on the total and conceptualization subscore of the DRS-2 and significantly improved on the Delis-Kaplan Executive Function System (DKEFS) Color-Word Interference and SDMT tasks while the sham group significantly increased their scores in the Trails making test, part B, and Boston Naming Test. There were no group differences in the perception of received treatment ($\chi 2$, $p = 0.31$), HADS depression, PDQ-39 or PDSS scores ($p > .10$). There were no significant adverse events (Supplementary Table 2).

Contrary to our hypothesis, bilateral DLPFC high-frequency rTMS did not improve cognitive functioning in PD-MCI, at least with the rTMS parameters chosen. It is possible that the beneficial effects of rTMS rely only on intact executive networks, as seen in PD with normal cognition (2) but not in PD-MCI where those networks demonstrate both structural and functional disruption (5). Alternatively, other cognitive targets such as the ventrolateral prefrontal cortex or frontoparietal networks may be more suitable due to their involvement in cognition and their dysfunction in PD (6). Lastly, if mood improvement is an important mediator of rTMS cognitive benefits, especially in the context of PD (7), our cognitive findings may be explained by our lack of rTMS benefit on mood and exclusion of depressed participants. Recommended outcome measures for PD dementia may not be translatable to PD-MCI trials (e1). It is possible that our primary outcome, the DRS-2, may have suffered from ceiling effects as average PD-MCI cut-points are over 90% of the maximum score (e2). While lack of change in other neuropsychological tests provides reassurance that our negative results were not entirely due to test selection, future studies may consider using outcomes specifically validated in PD-MCI populations (e3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

MCI	mild cognitive impairment
rTMS	repetitive transcranial magnetic stimulation
RMT	resting motor threshold
DLPFC	dorsolateral prefrontal cortex
DRS-2	Dementia Rating Scale-2
ATT	attention subscale of DRS-2

I/P	initiation/perseveration subscale of DRS-2
CONCEPT	conceptualization subscale of DRS-2
MEM	memory subscale of DRS-2
SDMT	symbol digit modalities test
BTA	brief test of attention.
MoCA	Monteral cognitive assessment
BNT	Boston Naming Test
UPDRS	Unified Parkinson’s disease rating scale
MFIS	Modified fatigue impact scale
PDQ	Parkinson’s disease questionnaire
HADS	Hospital anxiety and depression scale
PDSS	Parkinson’s disease sleep scale
CDR	clinical dementia rating
MMR	mixed model regression

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Table 1

Outcome measures at baseline and post ten-session intervention and between group differences.

	rTMS Mean ± SD Baseline	rTMS Mean ± SD Visit 10	rTMS Change *P* Value	Sham Mean ± SD Baseline	Sham Mean ± SD Visit 10	Sham Change *P* Value	Estimate	Standard Error	Degrees Freedom	*P* Value From MMR	95% CI	
DRS-2 Total	135.7 ± 3.5	134.3 ± 5.6	0.02	136.2 ± 5.4	136.2 ± 5.7	0.91	−2.07	1.23	46	0.1	−4.56	0.42
ATT	35.0 ± 1.6	35.6 ± 2.1	0.2	35.1 ± 1.6	35.2 ± 1.9	0.67	0.48	0.61	45.3	0.44	−0.76	1.71
I/P	35.5 ± 2.0	34.8 ± 3.6	0.14	35.5 ± 2.6	36.6 ± 0.9	0.068	−1.91	0.79	48.8	0.019	−3.5	−0.32
CONCEPT	36.7 ± 2.0	35.8 ± 1.9	0.026	36.3 ± 3.0	35.8 ± 3.0	0.3	−0.54	0.63	50	0.4	−1.81	0.73
MEM	22.5 ± 1.6	22.0 ± 1.7	0.15	23.3 ± 1.6	22.6 ± 2.3	0.14	0.19	0.54	44.9	0.72	−0.9	1.29
SDMT Oral	41.7 ± 12.5	42.7 ± 13.8	0.44	38.8 ± 13.1	47.0 ± 10.7	0.0009	−7.52	2.59	39.9	0.006	−12.76	−2.28
SDMT Written	35.0 ± 11.1	36.7 ± 12.1	0.002	36.2 ± 10.4	39.0 ± 9.8	0.0001	−1.26	0.98	46.7	0.2	−3.22	0.7
Color-Word Interference	77.0 ± 25.0	67.9 ± 12.1	0.042	72.3 ± 17.2	69.4 ± 20.5	0.15	−6.17	4.66	35.8	0.19	−15.61	3.27
Color-Word with Switching	85.5 ± 24.7	80.3 ± 20.3	0.27	90.6 ± 34.1	90.0 ± 30.9	0.96	−5.38	8.28	38.1	0.52	−22.15	11.39
BTA	14.0 ± 3.5	13.9 ± 4.4	0.9957	13.7 ± 4.0	14.3 ± 4.3	0.21	−0.74	0.82	48	0.37	−2.39	0.91
Letter Fluency	35.0 ± 11.7	35.3 ± 11.0	0.62	39.3 ± 15.1	40.3 ± 16.3	0.34	−0.38	2.28	43.5	0.87	−4.98	4.22
PDQ-39	37.3 ± 21.4	35.4 ± 21.4	0.64	37.0 ± 16.1	34.1 ± 21.6	0.24	−1.26	6.41	43	0.85	−14.2	11.69
PDSS	109.2 ± 21.3	112.3 ± 20.6	0.81	101.6 ± 18.4	104.6 ± 26.9	0.36	−7.78	7.33	42	0.29	−22.58	7.01
HADS Depression	5.6 ± 3.1	5.6 ± 3.5	1	4.6 ± 2.7	4.4 ± 3.2	0.59	0.19	0.62	42	0.76	−1.07	1.44
Trails B	121.2 ± 45.0	123.8 ± 70.3	0.89	139.2 ± 68.7	123.2 ± 58.6	0.02	19.58	12.7	41	0.13	−6.07	45.23
BNT	55.3 ± 5.0	55.5 ± 6.9	0.97	56.9 ± 2.4	58.3 ± 2.1	< 0.0001	−1.25	1.38	24.2	0.38	−4.1	1.6
CVLT Trial 5 Total	9.6 ± 2.9	9.0 ± 3.0	0.35	9.7 ± 2.8	8.2 ± 2.9	0.005	0.83	0.7	46.9	0.24	−0.57	2.23
CVLT Short Delay Cued Recall	9.0 ± 2.1	8.7 ± 3.3	0.55	8.1 ± 3.3	8.6 ± 3.4	0.21	−0.9	0.68	46.1	0.2	−2.27	0.48
CVLT Short Delay Free Recall	7.5 ± 3.1	6.3 ± 3.8	0.13	6.5 ± 3.3	6.3 ± 3.3	0.48	−0.62	0.71	41.6	0.39	−2.05	0.81
CVLT Long Delay Cued Recall	8.9 ± 2.7	8.6 ± 3.3	0.67	8.1 ± 3.6	8.3 ± 3.6	0.79	−0.42	0.83	44.4	0.62	−2.1	1.26
CVLT Long Delay Free Recall	7.5 ± 3.5	7.3 ± 4.2	0.87	7.2 ± 3.9	6.4 ± 4.1	0.22	0.91	0.91	46.8	0.32	−0.92	2.73
JLO	25.8 ± 4.9	26.7 ± 4.5	0.28	26.5 ± 4.5	27.5 ± 3.9	0.1	−0.44	0.96	49.7	0.65	−2.37	1.48

See manuscript for list of abbreviations. MMR: Mixed-model regression analysis. CI: confidence intervals. No significant group difference in baseline testing was found.