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Original Article

Treating Depression in Multiple Sclerosis with Transcranial Magnetic Stimulation: A Pilot Study

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ABSTRACT: ***Background:*** Depression is two to three times more common in people with multiple sclerosis (pwMS) than the general population. ***Objective:*** To evaluate the efficacy and tolerability of intermittent theta burst stimulation (iTBS) in treating depressive symptoms in pwMS and major depressive disorder (MDD). ***Methods:*** Twenty-one pwMS and MDD participated in an open-label 4-week trial of iTBS to the left dorsolateral prefrontal cortex (L-DLPFC). The Hamilton Depression Rating Scale (HAMD-17), California Verbal Learning Test Second Edition Total Learning (CVLT-II-TL), Brief Visuospatial Memory Test – Revised Total Learning (BVMT-R-TL) and Symbol Digit Modalities Test (SDMT) were administered before and after treatment. The primary outcome was response rates on HAMD-17, defined as a >50% reduction from baseline. ***Results:*** Depression scores decreased from baseline to post-treatment with a mean reduction of 10.24 points (d = 1.55, 95% CI 0.83 to 2.25, P < .001). Ten (58.8%) pwMS responded to treatment, and seven (41.2%) were non-responders (n = 17). The treatment response group showed lower depression scores post-treatment than non-responders (d = −3.01, 95% CI −4.43 to −1.55, P < .001). Post-treatment, responders showed higher visuospatial memory (d = 1.11, 95% CI 0.06 to 2.14, P = .039) and information processing scores (d = 1.74, 95% CI 0.58 to 2.87, P = .003) compared to non-responders. There were two drop-outs, and two participants were lost to follow-up. There were no serious adverse events. ***Conclusions:*** iTBS can improve depressive symptoms in pwMS and MDD and may be associated with cognitive improvement. ***Clinical trial registration:*** NCT04621708.

RÉSUMÉ : Le traitement de la dépression chez les personnes atteintes de sclérose en plaques, par la stimulation magnétique transcrânienne : résultats d'une étude pilote. ***Contexte :*** La dépression est de deux à trois fois plus fréquente chez les personnes atteintes de sclérose en plaques (SP) que dans la population générale. ***Objectif :*** L'étude visait à évaluer l'efficacité et la tolérabilité de la stimulation intermittente par salves d'ondes thêta (SISOT) dans le traitement des symptômes de dépression chez les personnes atteintes de SP et souffrant d'un trouble dépressif caractérisé (TDC). ***Méthode :*** Au total, 21 personnes souffrant de SP et d'un TDC ont participé à un essai de SISOT, non à l'insu, d'une durée de quatre semaines, ciblant le cortex préfrontal dorsolatéral gauche. Les sujets ont passé les tests suivants : l'Échelle de dépression de Hamilton (HAMD17), le California Verbal Learning Test 2nd Edition Total Learning, le Brief Visuospatial Memory Test – Revised Total Learning et le Symbol Digit Modalities Test, avant et après le traitement. Le critère d'évaluation principal était le taux de réaction favorable obtenu au test HAMD17, défini comme une réduction > 50 % du score par rapport au résultat initial. ***Résultats :*** La réduction moyenne des scores de dépression obtenus avant le traitement et après le traitement était de 10,24 points (d = 1,55; IC à 95 % : 0,83 à 2,25; $p <$ 0,001). Dix des personnes atteintes de SP (58,8 %) ont réagi au traitement [les sujets réactifs], tandis que sept autres (41,2 %) n'y ont pas réagi [les sujets non réactifs] (n = 17). Le groupe de sujets réactifs a obtenu des scores de dépression après le traitement inférieurs à ceux du groupe de sujets non réactifs (d = −3,01; IC à 95 % : −4,43 à −1,55; $p <$ 0,001). Par contre, les sujets réactifs ont obtenu, après le traitement, des scores de mémoire visuospatiale (d = 1,11; IC à 95 % : 0,06 à 2,14; p = 0,039) et de traitement de l'information (d = 1,74; IC à 95 % : 0,58 à 2,87; p = 0,003) supérieurs à ceux obtenus par les sujets non réactifs. Deux participants ont abandonné l'essai et deux autres ont été perdus de vue en cours de suivi. Enfin, il ne s'est produit aucun événement indésirable grave. ***Conclusion :*** Le traitement par stimulation intermittente par salves d'ondes thêta peut diminuer les symptômes de dépression chez les personnes atteintes de SP et de TDC, et pourrait même être associé à une amélioration des fonctions cognitives. ***Clinical trial registration:*** NCT04621708.

Keywords: cognition; depression; multiple sclerosis; transcranial magnetic stimulation

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Highlights

- People with multiple sclerosis (pwMS) and major depressive disorder (MDD) may experience improvements in depressive symptoms following intermittent theta burst stimulation (iTBS).
- iTBS treatment was safe and tolerable in pwMS and MDD; no serious adverse events were reported.
- pwMS who responded to iTBS also showed higher visuospatial memory and information processing post-treatment in comparison to non-responders.

Introduction

Depression is two to three times more common in people with multiple sclerosis (pwMS) than the general population.[1] Treatment with antidepressant medication and cognitive behavior therapy offer modest benefits.[1] Recent research has suggested that multiple sclerosis (MS) can be conceptualized as a network disorder.[2] Neuroimaging analyses demonstrated that functional connectivity between MS lesion sites and a pre-established depression circuit correlates with the severity of depressive symptoms in MS, and this association demonstrates greater specificity for depression than for other MS-related neuropsychiatric symptoms.[3] Furthermore, this MS depression circuit revealed a topographical similarity to an a priori identified depression circuit identified from stroke and penetrating head trauma lesions,[4] which aligned closely with the left dorsolateral prefrontal cortex (L-DLPFC)/subgenual cingulate cortex circuit implicated in the therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation for major depressive disorder (MDD).[5] This convergence of data suggests that MS depression may be responsive to the same L-DLPFC rTMS targets identified for primary MDD; however, there is currently a lack of rigorous research in this area. Establishing evidence of the safety and effectiveness of rTMS to the L-DLPFC may expand the currently limited evidence-based therapeutic options available for patients with MS experiencing depressive symptoms.[6,7]

The goals of this study are to investigate the safety and tolerability of intermittent theta burst stimulation (iTBS) rTMS to the L-DLPFC in improving depressive symptoms in pwMS and MDD. iTBS is an approved form of rTMS that involves brief protocols (~3 minutes per day) that has been shown to be equal in efficacy to longer (~37.5 minutes per day) high-frequency rTMS protocols to the L-DLPFC.[8] The antidepressant effects of L-DLPFC iTBS have been well established for MDD. The seminal non-inferiority THREE-D study reported a 49% antidepressant response rate and a 32% remission rate after 6 weeks of iTBS.[8] Meta-analyses of randomized control trials of L-DLPFC iTBS for MDD have subsequently confirmed the superiority of active versus sham stimulation in improving depressive symptoms.[9] Although iTBS rTMS is approved for use in MDD, there have been no safety and efficacy evaluations of this form of rTMS in MS patients with MDD. This study is the first report of iTBS rTMS to the L-DLPFC for depressive symptoms in MS.

It is hypothesized that L-DLPFC iTBS rTMS will be well tolerated by patients with MS and MDD and L-DLPFC iTBS will be associated with improvements in depressive symptoms. An exploratory hypothesis is that improvements in depressive symptoms with L-DLPFC iTBS rTMS will be associated with improvements in cognition function. This study contributes to the evaluation of the safety and tolerability of this potentially more rapid and accessible treatment for those suffering from MS and MDD.

Methods

Sample

Twenty-one pwMS and MDD participated in a single-center, open-label trial of iTBS rTMS delivered for just over three minutes to the L-DLPFC, five days a week for 4 weeks, for a total of 20 treatments. Inclusion and exclusion criteria appear in Table 1. MS and MDD diagnoses were verified by a neurologist and a psychiatrist, respectively.

Primary outcome measure

A reduction in depressive symptoms on the Hamilton Depression Rating Scale (HAMD-17)[10] from day 0 of treatment to the end of the 4-week trial. This was measured as a categorical response rates of $\geq$ 50% reduction from baseline HAMD-17. Remission rate was defined as HAMD-17 $\leq$ 7.

Secondary outcomes

Cognition was evaluated with serial versions of the Brief International Cognitive Assessment for MS (BICAMS)[11] containing the California Verbal Learning Test Second Edition Total Learning (CVLT-II-TL), the Brief Visuospatial Memory Test – Revised Total Learning (BVMT-R-TL) and the Symbol Digit Modalities Test (SDMT). Cognitive domains assessed include verbal memory, visuospatial memory and information processing, respectively. Participants were assessed at baseline and post-treatment.

Treatment

Resting motor threshold (RMT), defined as the minimum energy level delivered in single pulses to the left motor cortex which resulted in muscle activation of the thumb muscle (pollicis brevis) in the right hand in $\geq$ 50% of stimulations,[8] was empirically determined in each patient. RMT was determined through visual inspection, by consensus of the rTMS physician and the rTMS nurse. After determination of the RMT energy level and location, the coil was then advanced 5.5 cm anteriorly to target the L-DLPFC in a guideline-concordant manner.[12] In line with established iTBS rTMS protocols, stimulation was provided in triplet 50 Hz bursts, 2 second trains and with an intertrain interval of 8 seconds, for a total of 20 trains and 600 pulses per session.[8] The energy was delivered at 100% of RMT during the first treatment and then titrated to 110% on treatment day 2 and subsequently to 120% RMT for the remainder of the treatments, as tolerated.[8]

Side effects were determined by the Toronto Side-Effect Scale (TSES)[13] at weeks 2 and 4 after starting iTBS.

Statistical analysis

Between-group (depression responder versus non-responders) comparisons were undertaken with independent t-tests for continuous data and chi-square tests for categorical data. Paired *t*-tests were undertaken for longitudinal data (pre-and post-treatment). A between-group comparison of the Expanded Disability Status Scale (EDSS) was assessed with the Mann–Whitney *U* test. Cohen's *d* and 95% confidence intervals were provided where appropriate. *Z*-scores were obtained from Canadian normative data[14] for demonstrating the results graphically. All analyses were conducted using SPSS v.29.

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1 Men and women ≥18 and ≤70 years of age, inclusive.	1 Active substance abuse or dependence in the last 3 months, except nicotine.
2 History of MS confirmed by a neurologist.	2 Active suicidal intent.
3 Patients who are able and willing to give consent and able to adhere to treatment schedule and attend study visits, as determined by study psychiatrist.	3 Currently pregnant (as determined by history and serum HCG) or lactating.
4 DSM-V diagnosis of major depressive disorder (MDD).	4 A diagnosis of bipolar disorder.
5 Moderate severity with a Hamilton Depression Rating Scale (HAMD) at least 16.	5 A history of past or current psychotic symptoms.
6 Patients have had no increase or initiation of any psychotropic medication in the 4 weeks prior to screening.	6 Diagnosis of obsessive-compulsive disorder, post-traumatic stress disorder (current or within the last year), assessed by a study investigator to be primary and causing greater impairment than MDD.
7 Pass the TMS safety screening questionnaire.	7 Having failed a course of ECT in the current episode or previous episode.
8 Women of childbearing potential must agree to use a barrier contraception method throughout the study.	8 Previous trial of rTMS.
	9 Personality disorder deemed to be primary pathology.
	10 If participating in psychotherapy, must have been in stable treatment for at least 3 months prior to entry into the study, with no anticipation of change in the frequency of therapeutic sessions, or the therapeutic focus over the duration of the study.
	11 Clinically significant laboratory abnormality, in the opinion of the investigator.
	12 Unstable medical illness.
	13 Contraindication to rTMS, for example, presence of cardiac pacemaker, intracranial implant or metal in the cranium.
	14 Currently on more than 2 mg of lorazepam or equivalent.
	15 History of seizures, or currently on anticonvulsant for seizures.
	16 Concurrent use of a medication that may lower the seizure threshold, in the opinion of the investigator, for example, stimulant.

MS = multiple sclerosis; TMS = transcranial magnetic stimulation; rTMS = repetitive transcranial magnetic stimulation; DSM-V = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ECT = electroconvulsive therapy; HCG = human chorionic gonadotropin.

Results

Demographics and disease-related data

Average age was 45.53 (SD = 10.82) years; 76.5% were female; 94.1% had relapsing–remitting MS (RRMS); 94.1% were taking concurrent antidepressant medication; mean disease duration was 12.88 (SD = 7.64) years; mean years of education was 15.65 (SD = 2.21); median EDSS was 2.0 (range = 0–6.5). The mean time between treatment and assessment was 2.94 days (SD = 10.29). There were 10 (58.8%) treatment responders and seven (41.2%) non-responders ($n = 17$).

Demographic and disease-related comparisons between treatment responders and non-responders

There were no statistically significant between group baseline differences in age, sex, education, disease course and duration, EDSS and disease-modifying drug use (see Table 2). However, estimates of effects revealed that non-responders were older on average by 8.33 years ($d = -0.81$) and had MS for 7.97 years ($d = -1.19$) longer than responders.

Baseline psychometric comparisons between treatment responders and non-responders

There were no statistically significant baseline differences in scores on the HAMD-17, CVLT-II-TL, BVMT-R-TL and SDMT (see Table 3).

Post-treatment psychometric comparisons between treatment responders and non-responders

Depression scores decreased significantly from baseline to post-treatment with a mean reduction of 10.24 points (d=1.55, 95% CI 0.83 to 2.25, $P < .001$). Responders had significantly lower HAMD-17 scores post-treatment ($d = -3.01$, $P < .001$). Seven participants (41.2%) remitted post-treatment. Scores on the HAMD-17 declined by 14.80 points for responders from pre-($M = 21.30$, SD = 4.90) to post-treatment ($M = 6.50$, SD = 2.64, t [9] = 11.88, $P < .001$, $d = 3.76$) and by 3.71 points for non-responders from baseline ($M = 23.29$, SD = 4.39) to post-treatment ($M = 19.57$, SD = 6.05, t [6] = 3.36, $P = .015$, $d = 1.27$).

Responders had significantly higher BVMT-R-TL ($d = 1.11$, $P = .039$) and SDMT scores ($d = 1.74$, $P = .003$) than non-

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Table 2. Demographic and neurological comparisons between responders and non-responders

	Responders ($n = 10$)	Non-responders ($n = 7$)	Test statistic	Effect estimates (95% CI)	*P* value
Age, mean (SD), years	42.1 (7.4)	50.4 (13.5)	$t = -1.64$	−0.81 (−1.81 to 0.21)	.121
Education, mean (SD), years	16.1 (2.0)	15.0 (2.4)	$t = 1.01$	0.50 (−0.49 to 1.47)	.327
Disease duration, mean (SD), years	9.6 (4.6)	17.6 (8.9)	$t = -2.17$	−1.19 (−2.23 to −0.12)	.061
EDSS, median (range)	2.5 (1.0–6.0)	2.0 (0–6.5)	$U = 44.5$		.364
Female sex, *n* (%)	6 (60.0)	7 (100.0)	$x^2 = 3.66$		.103[a]
Disease course, *n* (%)			$x^2 = 1.52$		.412[a]
RRMS	10 (100.0)	6 (85.7)			
PPMS	0 (0.0)	1 (14.3)			
DMT use, *n* (%)	10 (100.0)	5 (71.4)	$x^2 = 3.23$		.154[a]

[a]Fisher's exact test. CI = confidence interval; SD= standard deviation; EDSS = Expanded Disability Status Scale; RRMS = relapsing–remitting multiple sclerosis; PPMS = primary progressive multiple sclerosis; DMT = disease-modifying therapy.

Table 3. Pyschometric comparisons between responders and non-responders at baseline and post-treatment

	Responders ($n = 10$)	Non-responders ($n = 7$)	Test statistic	Effect estimates (95% CI)	*P* value
Baseline					
HAMD-17, mean (SD)	21.3 (4.9)	23.3 (4.4)	$t = -0.86$	−0.42 (−1.39 to 0.56)	.405
CVLT-II-TL, mean (SD)	49.0 (10.6)	47.1 (5.8)	$t = 0.42$	0.21 (−0.77 to 1.17)	.682
BVMT-R-TL, mean (SD)	24.6 (4.5)	23.0 (3.9)	$t = 0.76$	0.38 (−0.61 to 1.34)	.458
SDMT, mean (SD)	51.7 (12.2)	40.3 (11.1)	$t = 1.97$	0.97 (−0.07 to 1.98)	.068
Post-treatment					
HAMD-17, mean (SD)	6.5 (2.6)	19.6 (6.1)	$t = -5.37$	−3.01 (−4.43 to −1.55)	<.001
CVLT-II-TL, mean (SD)	53.3 (9.8)	45.1 (18.0)	$t = 1.21$	0.60 (−0.40 to 1.58)	.245
BVMT-R-TL, mean (SD)	25.9 (5.3)	19.3 (6.8)	$t = 2.26$	1.11 (0.06 to 2.14)	.039
SDMT, mean (SD)	55.0 (13.3)	31.7 (13.5)	$t = 3.53$	1.74 (0.58 to 2.87)	.003

CI = confidence interval; SD= standard deviation; HAMD-17 = Hamilton Depression Rating Scale; CVLT-II-TL = California Verbal Learning Test Second Edition Total Learning; BVMT-R-TL = Brief Visuospatial Memory Test – Revised Total Learning; SDMT = Symbol Digit Modalities Test.

responders post-treatment. The CVLT-II-TL scores for the responders improved by 4.30 points from pre-($M = 49.00$, SD = 10.60) to post-treatment ($M = 53.30$, SD = 9.81, t [9] = −1.62, $P = .139$, $d = -0.51$). Responders showed higher BVMT-R-TL scores by 1.30 points from baseline ($M = 24.60$, SD = 4.48) to post-treatment ($M = 25.90$, SD = 5.30, t [9] = −0.95, $P = .366$, $d = -0.30$). Responders significantly improved scores on the SDMT by 3.30 points from pre-($M = 51.70$, SD = 12.19) to post-treatment ($M = 55.00$, SD = 13.29, t [9] = −3.01, $P = .015$, $d = -0.95$).

Non-responders showed decreased scores on the CVLT-II-TL by 2.00 points from baseline ($M = 47.14$, SD = 5.84) to post-treatment ($M = 45.14$, SD = 17.99, t [6] = 0.40, $P = .701$ $d = 0.15$). Non-responders' scores also decreased on the BVMT-R-TL by 3.71 points from pre-($M = 23.00$, SD = 3.92) to post-treatment ($M = 19.29$, SD = 6.78, t [6] = 1.56, $P = .169$ $d = 0.59$). Lastly, non-responders scored lower on the SDMT by 8.57 points from baseline ($M = 40.29$, SD = 11.13) to post-treatment ($M = 31.71$, SD = 13.49, t [6] = 1.65, $P = .149$ $d = 0.63$).

Serial CVLT-II-TL, BVMT-R-TL and SDMT *z*-score data are shown in Figure 1.

Two participants dropped out of the study: one due to discomfort and withdrawing consent, and the other due to the inability to establish RMT because of concurrent benzo usage. Both participants received another rTMS protocol outside of the study. Two participants were lost to follow-up. There were no serious adverse events.

Discussion

Current research has increasingly conceptualized psychiatric symptoms in MS as arising from disruptions in underlying neural networks. Evidence suggests that functional connectivity between MS lesion sites and a priori depression circuit derived from patients with focal brain lesions and other neuropsychiatric disorders is specific to depression symptomatology versus other MS-related symptoms.[3] This putative MS depression circuit includes the L-DLPFC, the most commonly used brain target of rTMS for the treatment of MDD.[15]

Our results revealed that a little over half (58.8%) the participants achieved an antidepressant response after 4 weeks of L-DLPFC iTBS. While a placebo effect is possible, our findings are consistent with the known trans-diagnostic effects of iTBS in treating depressive symptoms across a variety of neuropsychiatric disorders.[8] The tolerability of iTBS in treating depressive symptoms in our study adds to the safety profile of iTBS in

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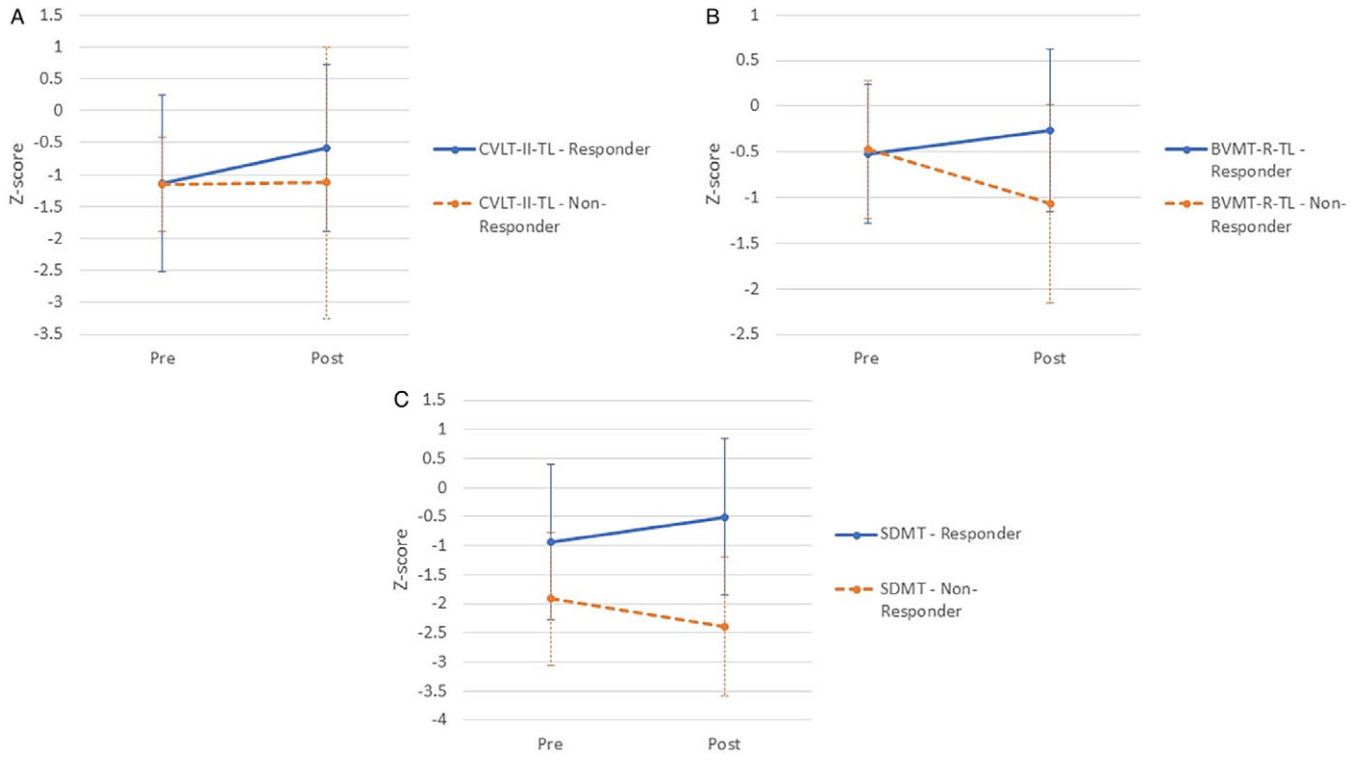


Figure 1. Mean (a) CVLT-II-TL, (b) BVMT-R-TL and (c) SDMT *z*-scores pre-and post-treatment by clinical response group. Error bars represent standard deviations. CVLT-II-TL = California Verbal Learning Test Second Edition Total Learning; BVMT-R-TL = Brief Visuospatial Memory Test – Revised Total Learning; SDMT = Symbol Digit Modalities Test.

pwMS. Previous MS research has reported the use of the iTBS to the motor cortex to treat spasticity, also with only limited side effects.[16] Taken together, these results suggest the iTBS rTMS is a promising and safe treatment strategy for depressive symptoms in pwMS.

An additional potential benefit to successfully treating depressive symptoms with rTMS may be improved cognition. Prevalence rates of cognitve dysfuction in pwMS range from 45% in RRMS to 70%–80% in people with progressive disease.[1] Cognitive rehabilition, considered the treatment of choice, may produce moderate benefits, most notably for memory and processing speed impairment.[17] Our pilot data suggest similar indices improving with rTMS treatment alongside depressive symptom lifting. In particular, statistically significant differences in visual memory and processing speed were seen between responders and non-responders. What is noteworthy about the serial processing speed data is that significant improvement occurred in the group that had a higher baseline SDMT, albeit not statistically. This turned out to be the group whose depressive symptoms responded to rTMS. Reasons for this are unclear and cannot be gleaned from pilot data, but it may be that individuals with MS and a higher cognitive reserve who become depressed are more responsive to treatment with rTMS. Future research is need to confirm or refute this intriguing possibility.

While studies have confirmed the cognitive safety of rTMS,[18] the salutary effect of rTMS on cognition has not been fully elucidated and remains an area of active study. A systematic review and meta-analysis examining the effects of rTMS to the L-DLPFC in a diagnostically heterogeneous sample of 174 studies encompassing 7905 patients with both psychiatric and neurological disorders found a small effect size for improvements in global cognition, declarative memory and working memory in the active versus sham rTMS groups; however, there were no effects on attention and language.[19] Another systematic review of the neurocognitive effects of theta burst stimulation for treatment-resistant depression in adults revealed cognitive improvement across specific domains including executive functioning, attention, working memory and verbal learning.[20] In contrast, other systematic reviews and meta-analyses which were restricted to comparing the effects of active versus sham rTMS on cognitive domains in those with MDD found no significant improvement in any cognitive domain.[21,22] The inconclusive findings for the effects of rTMS on cognitive systems may be the result of heterogeneity in subjects studied and stimulation protocols. As a result, it remains uncertain whether improvements noted with rTMS represent a direct effect of the stimulation on cognition, or whether improvements result from the indirect effect of improvement in mood with rTMS delivered to the L-DLPFC.[18,23]

This pilot study has some limitations. Our sample was limited in size and was primarily comprised of individuals with RRMS and low EDSS scores.

Conclusion

In summary, 4 weeks of L-DLPFC iTBS can improve depressive symptoms in pwMS and with it, aspects of cognition too. Treatment was generally well tolerated. In order to address the potential placebo response, these pilot data point the way forward to a more substantial randomized controlled trial that could have considerable clinical significance.

Data availability statement. The data that support the findings of this study are available upon reasonable request.

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Ethical standard. All subjects provided informed consent prior to participation. The study was approved by the research ethics board at Sunnybrook Health Sciences Centre.

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