Transcranial Magnetic Stimulation in Neuropsychiatry: An Update

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The potential of TMS as a treatment for cognitive disorders, fatigue, pain, and other manifestations of brain disease is discussed, as is the encouraging prospect for neuropsychiatric management of many patients.

Pharmacological management and behavioral interventions are currently the mainstay in the treatment of neuropsychiatric symptoms in neurological disease. However, a proportion of patients do not have significant improvement with these interventions. Repetitive transcranial magnetic stimulation (rTMS) has been shown to be effective in ameliorating treatment-resistant depression in both clinical trials and practice. Because of the related pathways that have been proposed in neuropsychiatric manifestations of neurological diseases, the therapeutic use of rTMS to alleviate depressive as well as other symptoms has been investigated in Alzheimer disease and mild cognitive impairment, fibromyalgia, multiple sclerosis, Parkinson disease, and cerebrovascular disease. This article reviews the use of rTMS as a treatment modality for neuropsychiatric symptoms in patients with these conditions (Table).

rTMS in Alzheimer disease and mild cognitive impairment
Available treatments for cognitive disorders are limited to slowing cognitive decline. rTMS has been proposed to modulate pathways related to cognition and has thus been studied in the context of Alzheimer disease and mild cognitive impairment. The largest trial investigated different rTMS protocols and the effects on global cognition: high-frequency (20 Hz, 90% motor threshold, 2000 pulses), low-frequency (1 Hz, 100% motor threshold, 2000 pulses), and sham stimulation.¹ The treatments were administered on the right and left dorsolateral prefrontal cortices 5 times daily for 5 days. Findings suggest that high-frequency rTMS provides more significant improvement than low-frequency rTMS and sham stimulation in global cognition, activities of daily living, and depression for 3 months. Similar results were found in 3 smaller studies in patients with Alzheimer disease (N = 8, 13, 12, respectively), which paired rTMS with cognitive training that stimulated up to 6 cortical regions. Brem and colleagues² and Rabey and colleagues³ used a sham control; Bentwich and colleagues⁴ did not. The correlation between rTMS and improvements in language difficulties was specifically explored. A controlled study of 15 patients with Alzheimer disease compared high-frequency rTMS (20 Hz, 90% motor threshold) with sham stimulation.⁵ The left and right dorsolateral prefrontal cortices during object and action naming were targeted. Improved action but not object naming was seen in the active-treatment group. Comparable results were seen in a study of 24 patients with Alzheimer disease.⁶ However, improved accuracy in both action and object naming was seen only in patients with moderate to severe decline. The researchers conducted another study in 10 patients with Alzheimer disease.⁷ High-frequency rTMS for 4 weeks was compared with 2 weeks of sham treatment followed by 2 weeks of active treatment (20 Hz, 100% motor threshold, 5 days a week). There was improvement in correct responses of auditory sentence comprehension with active treatment compared with both baseline and sham treatment. A double-blind randomized controlled trial (RCT) of 40 patients with mild cognitive impairment compared rTMS of the left dorsolateral prefrontal cortices (5 Hz, 80% motor threshold) with sham treatment.⁸ The researchers found that the active rTMS group had transient improvements in associative memory on face-name memory tasks immediately after stimulation. The effects of inhibitory rTMS (1 Hz, 90% motor threshold) and excitatory rTMS using intermittent theta burst stimulation (50 Hz, 80% motor threshold) on memory were compared in 8 patients with mild cognitive impairment and 100 healthy controls.⁹ Stimulation was applied over the left and right dorsolateral prefrontal cortices. The results showed that rTMS inhibition of the right dorsolateral
prefrontal cortices enhanced recognition memory for both healthy controls and patients with mild cognitive impairment. These studies are encouraging for the therapeutic role of rTMS in Alzheimer disease and in mild cognitive impairment. rTMS with or without cognitive training may enhance global cognition and function in the Alzheimer disease population. Specifically, the domain of language dysfunction studies has suggested improvements in naming and comprehension. Findings from studies on mild cognitive impairment indicate that rTMS may enhance associative and recognition memory. However, interpretation of the results is limited by the small sample sizes, inconsistencies in protocol, and heterogeneity in outcomes measured. Future research should focus on standardizing these aspects as well as consistently employing a sham control.

**rTMS in fibromyalgia**

The literature on rTMS in chronic pain conditions focuses largely on its potential for analgesia rather than neuropsychiatric outcomes; however, secondary outcomes have explored the effect on comorbid affective symptoms that are prominent in this disorder. A 2010 Cochrane Review concluded that high-frequency rTMS for chronic pain results in a small but consistent reduction in patient-reported pain scores compared with sham stimulation. Several fibromyalgia studies relevant to neuropsychiatric symptoms looked at rTMS and its effects on outcomes such as quality of life, mood, and cognition. A double-blind RCT consisting of 38 patients with fibromyalgia compared high-frequency rTMS (10 Hz, 90% motor threshold, 2000 pulses) with sham stimulation of the left primary motor cortex in 14 sessions over a 10-week period. Patients in the rTMS group had a statistically significant increase in quality of life, particularly in affective, emotional, and social dimensions. A small, randomized, sham-controlled trial of 15 women with fibromyalgia investigated the effects of high-frequency left motor cortex rTMS (10 Hz, 80% motor threshold) and low-frequency right dorsolateral prefrontal cortex rTMS (1 Hz, 110% motor threshold) on mood with 10 consecutive treatments. The depression symptoms in the low-frequency group were significantly decreased from baseline after 1 month of treatment. In the high-frequency group, depressive symptoms were significantly decreased immediately after rTMS, but the results were not sustained at 1-month follow-up. A double-blind, sham-controlled, randomized trial of 38 nondepressed patients with fibromyalgia looked at rTMS (10 Hz, 80% motor threshold) of the motor cortex and cognitive function. Patients were given weekly rTMS treatments over 11 weeks. Over time, a significant improvement in attention and executive function was observed in the rTMS group compared with the sham group; there were no differences in overall neuropsychological performance. Nor were there significant differences in sleep, depression, or anxiety scores in the active-treatment group. Adequately designed sham-controlled trials have suggested potentially therapeutic benefits of high-frequency rTMS in fibromyalgia. Further studies with larger enrollments will be necessary to confirm the positive findings in quality of life, mood, and cognition. Further research in other neuropsychiatric domains common in fibromyalgia (eg, fatigue, anxiety, concentration) is also warranted.

**rTMS in multiple sclerosis**

The therapeutic use of rTMS in multiple sclerosis has included investigation into spasticity, bladder dysfunction, and motor function. A disabling neuropsychiatric outcome that has been the subject of study is fatigue. Among the proposed etiologies, depression-related fatigue and cortical involvement may be implicated. A randomized sham-controlled trial with 28 patients who had multiple sclerosis used 18 sessions of deep high-frequency rTMS over 6 weeks; fatigue and depression were the primary outcomes. There were 3 groups: rTMS (18 Hz, 120% motor threshold) of the left prefrontal cortex, rTMS (5 Hz, 90% motor threshold) of the bilateral motor cortex, and sham stimulation. The group that received motor cortex stimulation showed a decrease (nonsignificant) in fatigue and a decrease (significant) in depressive symptoms 2 weeks after the first stimulation. Other placebo-controlled studies of magnetic field therapy that used modalities other than rTMS have been equivocal and showed both positive and negative results. Additional randomized sham-controlled trials are necessary to reach any conclusions about the role of rTMS in neuropsychiatric symptoms of multiple sclerosis.

**rTMS in Parkinson disease**

The therapeutic potential of rTMS in Parkinson disease, especially with regard to motor symptoms, has been studied. Investigations concerning treatment effects on neuropsychiatric symptoms relate largely to depression and global disease as measured by instruments such as the Unified Parkinson
Disease Rating Scale (UPDRS). Domains included in the UPDRS are mentation, behavior, mood, activities of daily living, and motor symptoms. Controlled trials have investigated the effects of rTMS in patients with Parkinson disease, but they have yielded mostly negative findings. In a double-blind RCT, 9 patients with Parkinson disease received low-frequency rTMS (1 Hz) on the vertex and 9 received sham stimulation for 10 days.16 The researchers found improvements in global Parkinson disease symptoms and depression in both groups. However, there were no improvements in sleep.

In a randomized sham-controlled trial of low-frequency rTMS (0.2 Hz, 110% motor threshold), 85 patients with Parkinson disease received motor cortical stimulation, occipital brain region stimulation, or sham stimulation once a week for 8 weeks.17 The results supported an improvement in global disease symptoms and depression; however, there were no differences between the groups. There was no improvement in subjective benefit reported by patients in any group. These results are in contrast to those from a previous trial of 15 patients with Parkinson disease in which the effect of low-frequency rTMS (0.2 Hz) to the frontal areas of the brain once weekly for 9 months was compared with that of sham treatment.18 The results showed that the active-treatment group (n = 8) had significant improvement in global disease and activities of daily living 3 months into the treatment, whereas the control group (n = 7) had no improvements. Similarly, observational studies without controls have reported positive results. A retrospective study followed 75 patients over 3 years.19 The results showed greater Parkinson disease deterioration in patients treated only with pharmacotherapy than in patients who had at least two 1-week rTMS (1 Hz) sessions each year in addition to pharmacotherapy. Moreover, these patients reported no adverse effects throughout the duration of the study. Other uncontrolled studies with small sample sizes (N = 11 and 6, respectively) show positive effects in global disease with 1-Hz rTMS to the vertex and 0.2-Hz rTMS in the frontal region.20,21

Numerous studies have investigated the effect of rTMS to left dorsolateral prefrontal cortices on depression in Parkinson disease. In a double-blind sham-controlled trial, 22 patients with Parkinson disease who had mild to moderate depression received rTMS (5 Hz, 90% motor threshold) for 10 days. Findings indicate a significant improvement in depression and global disease score at 30 days.22 RCTs also compared high-frequency rTMS to left dorsolateral prefrontal cortices in patients with Parkinson disease who had depression and were receiving fluoxetine. One study enrolled 21 patients who received either 5-Hz rTMS and placebo drug or sham rTMS and 20 mg/d of fluoxetine; the other study enrolled 42 patients who received either 15-Hz rTMS and placebo drug or sham rTMS and 20 mg/d of fluoxetine.23,24 Similar significant mood improvement was seen in both groups. Of note, there were fewer adverse effects associated with the rTMS treatment group.24 Some studies have investigated the potential benefits of single-session rTMS in patients with Parkinson disease. Three randomized, cross-over, sham-controlled trials each enrolled 10 patients with Parkinson disease. One trial compared single-session 10-Hz rTMS over the left dorsal premotor cortex and left dorsolateral prefrontal cortices and found no effect on global disease or cognitive function.25 Another trial compared single-session rTMS of right and left dorsolateral prefrontal cortices versus sham stimulation and found that active rTMS of the right dorsolateral prefrontal cortices was associated with significant enhancement of problem solving in spatial planning.26 Finally, the last trial found that single-session high-frequency rTMS over the left and right inferior frontal gyri resulted in increased speed of cognitive processing.27

Numerous studies have investigated rTMS as therapy for neuropsychiatric symptoms in Parkinson disease. Recent trials have failed to show significant differences in general disease symptoms between rTMS treatment groups and sham treatment groups. The interpretation is complicated by the small sample sizes, variability in rTMS frequency, and differences in area of stimulation. Double-blind sham-controlled trials of rTMS of the left dorsolateral prefrontal cortices have shown promising results. The trials suggest that the effects are comparable to those with fluoxetine, with less adverse effects. More trials are needed to clarify the efficacy of treatment of patients with Parkinson disease who have severe depression, including those who are treatment-refractory.

rTMS in cerebrovascular disease
Research on the neuropsychiatric outcomes of rTMS in patients with cerebrovascular disease have focused on alleviating depression. A randomized sham-controlled study enrolled 92 patients with vascular depression who had been unresponsive to medications.28 Antidepressant therapies were discontinued and the patients were randomized to receive 10 sessions of rTMS (10 Hz, 110% motor threshold) of left dorsolateral prefrontal cortices for 10 days, 15 sessions of rTMS (10 Hz, 110% motor threshold) of the left prefrontal cortex for 10 days, or sham treatment. Both active-treatment
groups had more significant improvement in depressive symptoms than the sham-treatment group, with more effect in the group that received left prefrontal cortex stimulation. A randomized sham-controlled study of 20 patients with treatment-refractory post-stroke depression compared 10 sessions of rTMS (10 Hz, 110% motor threshold) of the left prefrontal cortex over 2 weeks with sham treatment. A significant reduction in depression was noted in the active-treatment group compared with sham-treatment group. To date, studies have focused on the antidepressant benefit of high-frequency rTMS to the left prefrontal cortex in vascular depression and post-stroke patients. Future studies should focus on replicating these findings and extending investigations to other neuropsychiatric outcomes, such as cognition. These studies had strict inclusion criteria that made patients with systemic diseases ineligible, which limits the applicability to geriatric populations frequently seen in cerebrovascular disease.

**Summary**
The potential role of rTMS in treating neuropsychiatric symptoms of neurological disease has been expanding, especially in the past decade. Most of the studies have been related to Parkinson disease, mild cognitive impairment, and Alzheimer disease. In Parkinson disease, the findings are positive for improved depressive symptoms. However, results of recent trials that assessed the value of rTMS in alleviating global Parkinson disease symptoms are not as positive.

rTMS with or without cognitive training may enhance global cognition and function in patients with Alzheimer disease. The evidence in other areas, such as fibromyalgia, cerebrovascular disease, and multiple sclerosis, are more sparse and warrant further investigation. Current literature focuses on the antidepressant effects of rTMS in these conditions. Studies with larger sample sizes and control conditions will help confirm some of the initial findings. Future work is needed to delineate the optimal parameters of treatment for these disorders. Low-frequency stimulation (ie, less than 5 Hz) is thought to cause more of an inhibitory effect, while higher-frequency stimulation (ie, 10 Hz or more) is thought to be more of an excitatory paradigm. Other stimulation paradigms, such as theta burst stimulation, may be more potent at inducing neuroplastic changes than the standard low- and high-frequency stimulation and will be an area of investigation for the future.

![Table: Summary of major studies in rTMS for neuropsychiatric symptoms ...](image)

**Disclosures:**
*Mr Hsu is a student in the MD Program at the Faculty of Medicine of the University of Toronto, Dr Blumberger is Medical Head and Co-Director of the Temerty Centre for Therapeutic Brain Intervention and Campbell Family Research Institute at the Centre for Addiction and Mental Health (CAMH) in the department of psychiatry at the University of Toronto in Ontario. Mr Hsu reports no conflicts of interest concerning the subject matter of this article. Dr Blumberger receives research support from the Canadian Institutes of Health Research, the National Institute of Mental Health,*
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