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. 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 colleagues [2] and Rabey and colleagues [3] used a sham control; Bentwich and colleagues [4] 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. 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. 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. 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. 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. 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 (e.g., 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
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Threshold) of left dorsolateral prefrontal cortices for 10 days, 15 sessions of rTMS (10 Hz, 110%
vascular depression who had been unresponsive to medications.

Research on the neuropsychiatric outcomes of rTMS in patients with cerebrovascular disease have
parkinson disease who have severe depression, including those who are treatment-refractory.

Double-blind sham-controlled trials of rTMS of the left dorsolateral prefrontal cortices have shown
function.

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.

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. 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**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>[Ref1]</td>
<td>Depressive symptoms improved in Parkinson disease</td>
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<tr>
<td>[Ref2]</td>
<td>Cognition enhanced in Alzheimer disease</td>
</tr>
<tr>
<td>[Ref3]</td>
<td>Depression reduced in post-stroke depression</td>
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**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
References:


17. Okabe S, Ugawa Y, Kanazawa I; Effectiveness of rTMS on Parkinson’ Disease Study Group. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson’s disease. **Mov Disord.** 2003;18:382-388.


27. Srovnalová H, Marecek R, Rektorova I. The role of the inferior frontal gyri in cognitive processing of patients with Parkinson’s disease: a pilot rTMS study. **Mov Disord.** 2011;26:1545-1548.


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