Tourette syndrome (TS) is a chronic neuropsychiatric disorder occurring in early childhood or adolescence that’s characterized by multiple motor and vocal tics that are usually preceded by premonitory urges.\textsuperscript{1,2} Usually, the tics are repetitive, sudden, stereotypical, non-rhythmic movements and/or vocalizations.\textsuperscript{3,4} Individuals with TS and other tic disorders often experience impulsivity, aggression, obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder, and various mood and anxiety disorders.\textsuperscript{3} Psychosocial issues may include having low self-esteem, increased family conflict, and poor social skills. Males are affected 3 to 5 times more often than females.\textsuperscript{3} For most patients, the tics get less severe in late adolescence and early adulthood. However, approximately 10\% to 15\% of patients continue to experience chronic tics that are associated with significant disability.\textsuperscript{2,5-7}

There is no definitive treatment for TS. Commonly used interventions are pharmacotherapy and/or behavioral therapy, which includes supportive psychotherapy, habit reversal training, exposure with response prevention, relaxation therapy, cognitive-behavioral therapy, and self-monitoring. Pharmacotherapy for TS and other tic disorders consists mainly of antipsychotics such as haloperidol, pimozide, and aripiprazole, and alpha-2 agonists (guanfacine and clonidine).\textsuperscript{4,6-10} Unfortunately, not all children respond to these medications, and these agents are associated with multiple adverse effects.\textsuperscript{11} Therefore, there is a need for additional treatment options for patients.

Evidence is mixed, but rTMS might be an option for patients with treatment-resistant tics

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{A patient with Tourette syndrome}
\end{figure}

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Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive therapeutic technique in which high-intensity magnetic impulses are delivered through an electromagnetic coil placed on the patient’s scalp to stimulate cortical neurons. The effect is determined by various parameters, including the intensity, frequency, pulse number, duration, coil location, and type of coil.3,8

rTMS is FDA-approved for treating depression, and has been used to treat anxiety disorders, Parkinson’s disease, chronic pain syndromes, and dystonia.12,13 Researchers have begun to evaluate the usefulness of rTMS for patients with TS or other tic disorders. In this article, we review the findings of 11 studies—9 clinical trials and 2 case studies—that evaluated rTMS as a treatment option for patients with tic disorders.

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chae et al28 (2004)</td>
<td>Double-blind, sham-controlled, randomized controlled trial (N = 8) 5 days/outpatient</td>
<td>Total YGTSS score decreased by 24%, but not statistically significant (P = .068); improved Y-BOCS score (P = .01)</td>
<td>Small sample size, different frequencies, lack of direct measure of excitability/inhibition, prefrontal cortex location, high rTMS dose</td>
</tr>
<tr>
<td>Wu et al29 (2014)</td>
<td>Double-blind, sham-controlled, randomized controlled trial (N = 12) 2 days/outpatient</td>
<td>No significant decrease in YGTSS score (P = .43)</td>
<td>Small sample size with short treatment period, prior medication use, comorbidities</td>
</tr>
<tr>
<td>Münchau et al14 (2002)</td>
<td>Single-blind trial (N = 16) 4 weeks/outpatient</td>
<td>No significant improvement in MOVES/AYVS/MRVS scores or video-assessment scores of tics</td>
<td>Low stimulation intensity, short trains, small sample size, unilateral</td>
</tr>
<tr>
<td>Snijders et al15 (2005)</td>
<td>Single-blind trial (N = 5) 2 days/outpatient</td>
<td>No significant decrease in YGTSS score (P &gt; .05)</td>
<td>Low stimulation intensity, small sample size</td>
</tr>
<tr>
<td>Orth et al25 (2005)</td>
<td>Combined double-blind (N = 20) and open-label (N = 16) trial 3 weeks each/ outpatient</td>
<td>No significant difference in tic severity between active and sham group in double-blind randomized controlled trial phase (P = .27) but significant decrease in tic severity for open-label phase (P = .04)</td>
<td>Small sample size, short blinded phase, lack of patient-specific targeted procedure, bidirectional stimulation, use of psychotropics</td>
</tr>
</tbody>
</table>

AYVS: Adapted Yale Video Scale; MOVES: Motor tic, obsessions and compulsions, Vocal tic Evaluation Survey; MRVS: Modified Rush Video Scale; rTMS: repetitive transcranial magnetic stimulation; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; YGTSS: Yale Global Tic Severity Scale

A proposed mechanism of action

TS is believed to be caused by multiple factors, including neurotransmitter imbalances and genetic, environmental, and psychosocial factors.14 Evidence strongly suggests the involvement of the motor cortex, basal ganglia, and reticular activating system in the expression of TS.2,15-17

Researchers have consistently identified networks of regions in the brain, including the supplementary motor area (SMA), that are active in the seconds before tics occur in patients with these disorders.6,18-22 The SMA modulates the way information is channeled between motor circuits, the limbic system, and the cognitive processes.3,23-26 The SMA can be used as a target for focal brain stimulation to modulate activity in those circuits and improve symptoms in resistant patients. Recent rTMS studies that targeted the SMA have found that stimulation to this area may be an effective way to treat TS.19,20,23,27
rTMS for tic disorders

We reviewed the results of 11 studies that described the use of rTMS for TS and other tic disorders. They included:

- 2 double-blind, randomized controlled trials
- 2 single-blind trials
- 1 double-blind trial with an open-label extension
- 4 open-label studies
- 1 case series and 1 case report

Study characteristics. In the 11 studies we reviewed, the duration of rTMS treatment varied from 2 days to 4 weeks. The pulses used were 900, 1,200, 1,800, and 2,400 per day, and the frequencies were 1 Hz, 4 Hz, 15 Hz and 30 Hz. Seven studies did not use placebo- or sham-controlled arms. Although several different scales were used to measure outcomes, many of the studies employed the Yale Global Tic Severity Scale (YGTSS), and effectiveness of rTMS was defined as a significant reduction in the YGTSS score.

Efficacy. Two double-blind trials found no significant improvement in tic severity in patients treated with rTMS. In addition, the 2 single-blind studies showed no beneficial effects of rTMS for patients with OCD and TS. However, in 6 patients with OCD and TS there was a significant improvement in YGTSS score.

Clinical Point
rTMS might improve symptoms of OCD that co-occur with tic disorders

rTMS for tic disorders: Summary of open-label trials and case reports

<table>
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<th>Study</th>
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<tr>
<td>Mantovani et al 23 (2006)</td>
<td>Open-label trial (N = 10) 2 weeks/outpatient</td>
<td>Significant decrease in YGTSS score (P = .005) and YBOCS score (P = .001)</td>
<td>Open-label trial with small sample, no placebo group, concomitant medications</td>
</tr>
<tr>
<td>Kwon et al 30 (2011)</td>
<td>Open-label trial (N = 10) 2 weeks/outpatient</td>
<td>Significant improvement in YGTSS score (P = .012)</td>
<td>Small sample size, no control group/open-label trial, lack of direct measure of excitability/inhibition, longer tics duration, concomitant medications</td>
</tr>
<tr>
<td>Le et al 3 (2013)</td>
<td>Open-label trial (N = 25) 4 weeks/outpatient</td>
<td>Significant decrease in YGTSS score (P = .001)</td>
<td>Open-label trial, small sample size, no control group, concomitant medications</td>
</tr>
<tr>
<td>Bloch et al 8 (2016)</td>
<td>Open-label trial (N = 12) 4 weeks/outpatient</td>
<td>Overall no improvement in YGTSS score (P = .302). However, in 6 patients with OCD and TS there was significant improvement in YGTSS score (P = .037).</td>
<td>Open-label study, small sample size, severely ill patients</td>
</tr>
<tr>
<td>Mantovani et al 27 (2007)</td>
<td>Case series (N = 2) 2 weeks/not reported</td>
<td>Significant decrease in YGTSS score</td>
<td>No sham-control, case series, only 2 patients</td>
</tr>
<tr>
<td>Salatino et al 31 (2014)</td>
<td>Case report (N = 1) 2 days/not reported</td>
<td>Improvement in all scales and decreased frequency of weekly self-injurious behaviors</td>
<td>Case report, only 1 patient</td>
</tr>
</tbody>
</table>

OCD: obsessive-compulsive disorder; TMS: repetitive transcranial magnetic stimulation; TS: Tourette Syndrome; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; YGTSS: Yale Global Tic Severity Scale
tic severity in a subgroup of patients suffering from comorbid OCD.8,28

Safety profile and adverse effects. In the studies we reviewed, the adverse effects associated with rTMS included headache (45%),1,8,24,26,28,29 scalp pain (18%),8,30 self-injurious crisis (9%),31 abdominal pain (9%),23 red eyes (9%),29 neck pain (9%),1 muscle sprain (9%),1 tiredness (9%),24,26 and increase in motor excitability (9%).28 There were no severe adverse effects reported in any of the studies. The self-injurious crisis reported by a patient early in one study as a seizure was later ruled out after careful clinical and electroencephalographic evaluation. This patient demonstrated self-injurious behaviors prior to the treatment, and overall there was a reduction in frequency and intensity of self-injurious behavior as well as an improvement in tics.31

Dissimilar studies
There was great heterogeneity among the 11 studies we reviewed. One case series27 and one case report31 found significant improvement in tics, but these studies did not have control groups. Both studies employed rTMS with a frequency of 1 Hz and between 900 to 1,200 pulses per day. Three open-label studies that found significant improvement in tic severity used the same frequency of stimulation (1 Hz with 1,200 pulses per day).3,23,30 All studies we analyzed differed in the total number of rTMS sessions and number of trains per stimulation.

The studies also differed in terms of the age of the participants. Some studies focused primarily on pediatric patients,3,30 but many of them also included adults.

The main limitations of the 11 studies included a small sample size,1,3,3,23-25,28-30 no placebo or controlled arm,1,3,23,27,30,31 concomitant psychiatric comorbidities8,28,29 or medications,1,3,22,29,30 low stimulation intensity,24-26 and use of short trains24,26 or unilateral cerebral stimulation.24,26 Among the blinded studies, limitations included a small sample size, prior medications used, comorbidities, low stimulation intensity, and high rTMS dose.1,24-26,28,29

A possible option for treatment-resistant tics
We cannot offer a definitive conclusion on the safety and effectiveness of rTMS for the treatment of TS and other tic disorders because of the inconsistent results, heterogeneity, and small sample sizes of the studies we analyzed. Higher-quality studies failed to find evidence supporting the use of rTMS for treating TS and other tic disorders, but open-label studies and case reports found significant improvements. In light of this evidence and the treatment’s relatively favorable adverse-effects profile, rTMS might be an option for certain patients with treatment-resistant tics, particularly those with comorbid obsessive-compulsive symptoms.

Bottom Line
The evidence for using repetitive transcranial stimulation (rTMS) to treat patients with Tourette syndrome and other tic disorders is mixed. Higher-quality studies have found no significant improvements, whereas open-label studies and case studies have. Although not recommended for the routine treatment of tic disorders, rTMS may be an option for patients with treatment-resistant tics, particularly those with comorbid obsessive-compulsive symptoms.
References


