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Randomized sham controlled double-blind trial of repetitive transcranial magnetic stimulation for adults with severe Tourette syndrome

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Abstract

Background—A small proportion of individuals with Tourette syndrome (TS) have a lifelong course of illness that fails to respond to conventional treatments. Open label studies have suggested that low frequency (1-Hz) repetitive transcranial magnetic stimulation (rTMS) targeting the supplementary motor area (SMA) may be effective in reducing tic severity.

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Conflicts of interest:

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Objective/Hypothesis—To examine the efficacy of rTMS over the SMA for TS in a randomized double-blind sham-controlled trial (RCT).

Methods—We conducted a two-site RCT-rTMS with 20 adults with severe TS for 3 weeks. Treatment consisted of 15 sessions (1-Hz; 30 min; 1,800 pulses per day) of active or sham rTMS at 110% of the motor threshold over the SMA. A subsequent 3 week course of active rTMS treatment was offered.

Results—Of the 20 patients (16 males; mean age of 33.7 ± 12.2 years), 9 received active and 11 received sham rTMS. After 3 weeks, patients receiving active rTMS showed on average a 17.3% reduction in the YGTSS total tic score compared to a 13.2% reduction in those receiving sham rTMS, resulting in no statistically significant reduction in tic severity ($p=0.27$). An additional 3 week open label active treatment for those patients ($n = 7$) initially randomized to active rTMS resulted in a significant overall 29.7% reduction in tic severity compared to baseline ($p=0.04$).

Conclusion—This RCT did not demonstrate efficacy of 3-week SMA-targeted low frequency rTMS in the treatment of severe adult TS. Further studies using longer or alternative stimulation protocols are warranted.

Keywords

Tourette syndrome; transcranial; magnetic stimulation; randomized controlled trial

Introduction

Tourette syndrome (TS) is a childhood onset neuropsychiatric disorder characterized by chronic motor and vocal tics that are often preceded by premonitory urges [1]. Although the tic symptoms in the majority of children with TS improve during adolescence, adults with persistent illness can experience chronic and severe tics [1, 2]. As early as the 1980s, Eccles speculated that the Supplementary Motor Area (SMA) was involved with the intentional preparation to move [3]. More recently, event related fMRI techniques have implicated the SMA in the preparation and organization of voluntary movements [4]. Not only does stimulation of this region produce both movements and urges to move (reminiscent of the premonitory urges of TS), but the nature of the movements or corresponding urges range from simple motor acts to complex movements, paralleling the range of simple to complex tics experienced in TS [1]. Neuroimaging studies examining patterns of brain activation in individuals with TS have consistently identified the SMA as one of the structures that is active in the seconds preceding tics [2, 5, 6].

Randomized controlled trials (RCTs) have documented the efficacy of several behavioral and pharmacological treatments for TS [7, 8]. However, approximately one-third of individuals with TS do not benefit from first-line treatments, and several of the most effective medications used to treat tics have significant side effects [9, 10]. Experimental use of deep brain stimulation (DBS) surgery has been shown to produce positive results for a proportion of adults with severe, refractory TS [11, 12].

However, to date there have not been any RCT documenting the safety and efficacy of DBS and the optimal site for electrode placement has yet to be determined. In addition, DBS can

be associated with serious adverse effects including an increased risk of infection [13]. In this context, novel, less-invasive treatments to reduce tic severity are urgently needed, especially for adults with severe, refractory TS.

Transcranial magnetic stimulation (TMS) is a noninvasive means of stimulating targeted accessible cortical regions [14]. Initial repetitive TMS (rTMS) studies targeting motor and premotor cortical sites with either 1-Hz or 15-Hz have had limited or no success in treating individuals with severe TS [see Table 1; 15, 16]. More recently several open studies have reported that low frequency (1-Hz) rTMS targeting the SMA can decrease the frequency and intensity of tics [17–22]. Recently, Wu et al. reported the results of a RCT in 12 individuals with TS using continuous theta burst stimulation (cTBS) to the SMA. However, after two daily sessions no significant differences in tic severity ratings were detected [23].

The goal of this two-site RCT was to examine the efficacy of low-frequency rTMS targeting the SMA bilaterally for reducing tic severity in 20 adults with severe TS. 1-Hz rTMS was delivered daily with each session lasting 30 minutes (1,800 pulses per day) at 110% of the motor threshold 5 days a week, for 3 weeks in the double-blind phase (phase 1) and up to six weeks in an extended open label phase (phase 2).

Methods

Recruitment and participants

Subjects were recruited at two sites (Yale Child Study Center and Columbia University). Men and women 18 years or older who met DSM-IV TR criteria for Tourette syndrome were eligible to participate. TS needed to be the most problematic neuropsychiatric disorder and the primary reason for seeking treatment. Patients had to score moderately ill or worse as rated on the Clinical Global Impression Severity scale (CGI-S) [24]. On the Yale Global Tic Severity Scale (YGTSS) their total motor tic or vocal tic severity had to be above 20 [25]. They also needed to have a persistent high level of tic severity for 4 months despite efforts to control their tics using medications OR the presence of self-injurious tics as judged by two independent clinicians. They also needed to be either unmedicated or on stable medication treatment for tics, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and/or depressive disorder for at least six weeks, with no planned changes for the entire duration of the study. Patients were excluded if they were diagnosed with severe current major depressive disorder (MDD) [defined as Hamilton Depression Rating Scale-24 (Ham-D-24) >16][26], exhibited significant acute suicide risk, or had a history of bipolar disorder, of any psychotic disorder, or of substance abuse or dependence within the past year. Patients with other neurological disorders, increased risk of seizure, use of proconvulsant medications (such as, bupropion, maprotiline, and tricyclic antidepressants), implanted devices, metal in the brain, unstable medical conditions, pregnancy, or breast-feeding were excluded. We also excluded patients with prior TMS exposure to reduce risk of unblinding.

Of the 45 subjects screened, twenty subjects (16 males and 4 females; mean age of 33.7 ± 12.2 years) who met study criteria and were willing to comply with the time schedule, were recruited between July 2007 and October 2010 from the Tic Disorder Specialty Clinic, Child

Study Center, Yale University and from the Brain Behavior Clinic of New York State Psychiatric Institute, Columbia University (Table 1). Of these, 2 did not complete the study because of competing time commitments and long travel times. Analyses were conducted on the entire sample (9 in the active group and 11 in the sham group, last time point carried forward) and on the 18 completers (Supplemental Figure A).

Baseline Assessments

At Baseline the YGTSS, a clinician-rated scale, was used to assess both motor and vocal tic severity [25]. The primary outcome measure in this study is the YGTSS Total Tic Score, as it shows the greatest sensitivity to change in tic severity over brief periods of time [27]. In addition patients completed the Premonitory Urge Tic Scale (PUTS) which is a self-report questionnaire designed to assess the presence of premonitory sensory urges [28].

Other rating scales included the CGI-S [24] which is a clinician-rated scale that has been used in several studies with TS patients [29, 30]. To rate frequently co-occurring conditions we used: (1) the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). This is a clinician-rated scale that rates the severity of obsessions and compulsions on time spent, interference, distress, resistance, and control [31]; (2) The Adult ADHD Self-Report Scale (ASRS-v1.1) was developed as an assessment tool to aid in the diagnosis of ADHD in adults and adolescents [32, 33]; and (3) the 24 item Hamilton Depression Rating Scale (Ham-D 24) and the Hamilton Anxiety Rating Scale (Ham-A). Both are commonly used clinician-measures of depression and anxiety respectively [26, 34].

Other assessments at baseline

The initial medical assessment included a full physical and neurological examination, laboratory studies (CBC with an automated differential, electrolytes, glucose, creatinine, LFTs, U/A, a urine pregnancy test [if female], and urine toxicology screen at baseline only) and EKG. If the toxicology screen was found to be positive, the results were destroyed and the subject was not enrolled in the study. At baseline, we also administered the Transcranial Magnetic Stimulation Adult Safety Screen (TASS) developed by Keel et al. which collects specific information concerning the potential risks associated with rTMS [35].

Outcome measures and response criteria

Patients were evaluated every week by raters blind to treatment assignment and also completed self-rating forms at the end of each week of treatment. Clinical measures included: YGTSS, PUTS YBOCS, ASRS, and the CGI-S. The primary efficacy measure was the YGTSS. Patients with a 25% YGTSS reduction were classified as responders [32].

rTMS methods

Patients were randomized to receive active rTMS or sham treatment. Randomization was performed by site at the Yale-New Haven Hospital Investigational Pharmacy.

Motor Threshold—Resting MT was defined as the minimum magnetic flux needed to elicit a threshold EMG response (50 μ V in peak-to-peak amplitude) in a resting target muscle (*abductor pollicis brevis*) in 5/10 trials using single-pulse TMS administered to the

contralateral primary motor. This measurement was obtained at the beginning of every week, on every subject. The coils would then be “switched” by an unblinded person so that the treating clinicians and subjects would remain blinded to what the subject was supposed to receive.

Active rTMS—rTMS was administered with the Magstim super-rapid stimulator (Magstim Company Ltd, UK) using a vacuum cooled 70-mm figure-of-eight coil. Stimulation parameters were 1-Hz, 110% of resting MT (using the lowest value obtained independent of hemisphere), for 30-minutes (1,800 pulses/d) once a day, 5 days/week, for 3 weeks (in phase 1) to 6 weeks (in phase 2). The coil was positioned over the anterior SMA using the International 10–20 EEG System coordinates [14]. The rTMS target was defined at 15% of the distance betweeninion and nasion anterior to Cz (vertex) on the sagittal midline. Brainsight TMS navigation system was used at both sites to locate and monitor on-line the stability of coil placement during each rTMS session. The coil was placed with the handle along the sagittal midline, pointing towards the occiput to stimulate bilaterally and simultaneously the SMA.

Blinding—Sham rTMS was administered using the Magstim sham coil which contains a mu-metal shield that diverts the majority of the magnetic flux so that a minimal (<3%) magnetic field is delivered to the cortex [33]. This coil looks and sounds like an active coil; however, it does not feel like active rTMS, which generates a tapping sensation on the scalp. In order to maintain the blind, we kept the raters blinded to treatment condition and created a separation between clinical team and rTMS treating physician(s). We also excluded patients who had received r TMS treatments in the past. At the end of each week of treatment, the patients and the blind clinical evaluators were asked to “guess” whether or not they had been receiving active or sham rTMS. They were also asked to rate their confidence in this judgment on a five point scale (“extremely”, “considerably”, “moderately”, “slightly” or “not at all”).

Side-effect ratings

Before and after each session patients were asked a series of questions in a structured form in order to rate TMS side-effects. In addition subjects were asked to complete the systematic Assessment for Treatment Emergent Effects (SAFTEE) [36].

Statistical analyses

Statistical analyses were performed using the SAS 9.3 (SAS Institute, Inc., Cary, NC). Baseline characteristics were compared between groups using t-tests for continuous variables and chi-square tests for categorical variables. Mixed model repeated measures analysis with baseline scores as a covariate was used to test the effect of treatment on the primary outcome, YGTSS. Treatment, visit and site (along with corresponding interactions) were included in the model as fixed effects and subject was entered as a random effect. For the primary outcomes, an intention-to- treat analysis was performed with the last data point carried forward. The same approach was used to evaluate the effects of treatment on the secondary outcomes: PUTS, YBOCS and ADHD rating scale. Baseline to end-point comparisons were performed using paired t-tests. The proportion of responders to treatment

was tested using Fisher's exact test. Pearson correlations were used to examine the association between change in clinical response and physiological measures.

Results

Recruitment and retention

Of the 45 patients screened, 39 were eligible for the study, but only 20 were randomized and assigned to either active or sham rTMS (Supplemental Figure A). Ten of the eligible patients decided not to participate because of the five day a week schedule and the travel time needed as some patients lived at a considerable distance from either of the two treatment sites. Nine had other reasons.

Demographics and baseline clinical characteristics of the study population

As shown in Table 2, the active and sham groups did not differ significantly in demographics or baseline clinical ratings. The baseline data also did not differ when stratified by site. A total of 10 patients (4 randomized to Active rTMS and 5 randomized to the Sham group) were on at least one psychotropic medication during the course of the study (Table 2). Eight patients were on multiple psychotropic medications.

Randomized phase (phase 1)

Twenty patients entered and 18 completed phase 1 (3-week double-blind phase). The two, who did not complete phase 1, had difficulty meeting the required treatment schedule because of long commute times and other competing demands on their time.

Phase 1 clinical data of individuals randomized for active or sham rTMS are presented in Table 3. No significant differences on YGTSS, PUTS, YBOCS or ASRS were detected between active vs. sham rTMS over time. Repeated-measures analysis revealed no significant main effect of time on the clinical scores. No site effect was evident. Likewise, no significant time $\times$ group $\times$ site interactions were seen.

Regarding the 20 patients who met criteria for TS, a 33% (3/9) response rate was observed in those randomized to active rTMS and 18% (2/11) with sham rTMS (Fisher's exact test, $p=0.62$). Analysis of 18 completers showed a response rate of 37.5% (3/8) with active and 20% (2/10) with sham rTMS (Fisher's exact test, $p=0.61$) at the end of phase 1. None of the three responders to active rTMS were on neuroleptics, serotonin reuptake inhibitors, benzodiazepines, or anticonvulsants.

Remarkably, one of the patients at the Columbia site showed a dramatic improvement from a total tic score on the YGTSS of 30 at baseline down to 8 (and a YGTSS impairment score of 0) at the end of the third week. However, his symptoms were back at the baseline level 2 months after completing the trial. This was also the only responder in the active rTMS group on a psychotropic medication (guanfacine). This patient also did not elect to continue rTMS treatment in the open phase. One of the two responders in the sham group was on a combination of haloperidol, clomipramine, and oxcarbazepine. The other responders in the sham group were not taking any psychotropic medication (see supplementary Table A). Two patients discontinued the intervention before completing phase 1 (1 active, 1 sham).

Five patients (3 randomized to active rTMS) had clinically significant OCD symptoms at the baseline. Two of them (both in active rTMS group) had a positive response (at least 25% of decrease of YBOCS baseline scores) upon completion of phase 1. Eight patients (5 randomized for active rTMS) fulfilled current ADHD diagnosis at baseline. None of them were responders with regard to the observed change in the severity of their ADHD symptoms (defined as a 25% reduction in their ADHD Rating Scale scores).

Overall the blind was maintained reasonably well. Using a threshold of “considerably confident” or “extremely confident”, the blind clinicians were correct in their judgment, active vs. sham, only 14% of the time. The patients did slightly better and were correct 24% of the time.

Open-label phase (phase 2)

Of 18 patients eligible to continue, 17 patients entered and 16 completed the open-label phase (seven from the active phase 1 group and nine from the sham phase 1 group). Demographics, symptoms ratings, and MT of those entering the open-label phase did not differ significantly from those who did not enter this phase.

Nine patients initially randomized to sham had no significant change in their YGTSS total tic scores after 3 weeks of active rTMS (from 32.9 ± 8.4 to 31.8 ± 8.5 ; $F = 0.64$, $df = 2, 16$, $p = 0.54$). Seven patients initially randomized to active who received an additional 3-week active rTMS showed further improvement (though not statistically significant) from week 3 to week 6 on the YGTSS total tic scores (from 31.1 ± 9.5 to 25.3 ± 6.7 , $F = 0.58$, $df = 2, 12$, $p = 0.57$). However, the mean improvement in the total tic severity score from baseline to 6 weeks [mean reduction of YGTSS score = 10.7 points (29.7%)] for the 7 patients who completed full 6 weeks of active treatment was statistically significant ($t = 2.6$, $df = 6$, $p = 0.04$). Of these 7 patients three were judged to be responders. One responder showed a further incremental improvement in tic severity going from a YGTSS total tic score of 41 at baseline to 26 at three weeks and 12 at six weeks. The two other responders at six weeks only showed a clear reduction in tic symptoms after the full six weeks of rTMS treatment (see Supplemental Table A). One of these responders was taking a combination of haloperidol; paroxetine; clonazepam; and quetiapine. The third responder was not taking any psychotropic medications during the trial. In the open phase, three of the patients initially randomized to sham treatment were judged to be responders after 3 weeks of active rTMS treatment. Two of these patients were not taking any psychotropic medications during the trial. The third responder at six weeks was taking a combination of clonidine; risperidone; and valproic acid for the duration of the trial (see Supplemental Table A). Among the four non-responders two were not taking psychotropic medications and two were (clonazepam in one case and a combination of fluoxetine and lamotrigine).

Motor Threshold (MT)

Cortical excitability measures across phase 1 are presented in Table 4. After 3 weeks patients receiving active rTMS over the SMA had a significant mean reduction change in their right MT, while sham group did not ($t = 2.32$, $df = 16$, $p = 0.034$). For the 6 of the 7 patients who received active rTMS for 6 weeks the right MT mean (SD) went from 63.3

(14.1) at baseline to 58.0 (9.3) at 6 weeks ($t=2.4$, $df=5$, $p=0.06$). After 3 weeks the change in the right MT was not associated with changes in their YGTSS tic scores. However, the change in the right MT (baseline to 6 weeks) was associated with changes in their YGTSS tic scores from ($r=-0.91$, $p=0.004$). Similarly, a significant association was also seen for the change in the right MT and the change in the YGTSS tic scores from 3 to 6 weeks ($r=-0.80$, $p=0.032$). Left MT did not show any changes following either active or sham treatments (Table 4).

Safety

The TMS sessions were safe and well tolerated for most patients. There were no seizures, neurological complications, or subjective complaints about memory or concentration impairments. Headache, neck pain and muscle sprain were the only side effects reported as “severe” in active treatment. But only in one instance was a “severe” side effect, i.e., a severe headache, judged to be treatment related (Supplemental Table B). On the first treatment day of phase 1, this subject could not tolerate the coil and it resulted in severe headache. The treatment was stopped and the headache remitted with paracetamol 500mg PO. This case was discussed between both sites and it was decided to gradually increase the percent intensity of the MT from 80% until achieving the targeted 110% so that the subject would adjust to the “tapping” of the coil.

Discussion

This double-blind sham-controlled clinical trial is the largest trial to date using low-frequency rTMS for the treatment of TS using the SMA as the stimulation target. In addition, to our knowledge, this is the first study using an administration period of 3 to 6 weeks to treat TS. Compared to sham stimulation, rTMS treatment did not induce a significant tic reduction during the blinded phase of the study. Changes in the ratings of premonitory urges, OCD, and ADHD symptoms also did not significantly improve. Our results do not confirm the robust results of the earlier open trials using the SMA as the target (Table 1). However, we recruited adult patients with chronic, severe TS whereas some of the open trials focused on children and adolescents with lower levels of YGTSS at baseline [15–17]. Earlier plasticity studies have shown that adults with TS have decreased physiologic responses in motor areas to both excitatory and inhibitory TMS [39, 40]. In addition, symptom chronicity and severity have been shown to be predictors of poor response in TS and this may be true for rTMS as well [2, 10].

However, a sizable proportion of the TS subjects who received active rTMS for 6 weeks were judged to be responders (57.1%). Moreover, the mean improvement in the YGTSS total tic severity score from baseline to week 6 was statistically significant. While this could partially be a placebo effect, it is possible that some adult patients with severe TS may require a longer duration of rTMS administration before clinical improvement is evident.

We proposed the SMA as a useful target for inhibitory stimulation and found a decrease in TS patients’ right hemisphere MT after active rTMS but no change with sham. In addition, significant negative correlations were observed at 6 weeks between the changes in tic severity and the right MT. Left hemisphere MT was not affected by either active or sham

rTMS. Both of these observations point toward a lateralized effect of bilateral rTMS to the SMA on the right motor system.

Other studies suggest abnormal brain activity in the right hemisphere of TS patients [41], and particularly in the right frontal pole [42], with findings of hyper-excitability of motor regions [43–47]. The fact that 1-Hz rTMS resulted in a decrease in motor cortex excitability might suggest a possible failure of the active treatment in affecting inhibitory circuits that could not have been up-regulated by the parameters used in our study. It has been shown that intensity-dependent effects of 1-Hz rTMS on human corticospinal excitability with suprathreshold (i.e., 115% of MT) stimulations are capable of reducing the size of motor evoked potentials [48]. Other patients, such as those affected by migraine, where impairment of inhibitory intracortical circuits [49] would suggest the use of low frequency rTMS, showed a clinically significant decrease of migraine attacks after 1-Hz rTMS [50], and an increased cortical excitability in both occipital and motor areas [51, 52]. Considering that imaging studies have demonstrated that 1-Hz rTMS might produce increases in brain activity locally and in associated brain areas [53], the question about whether 1-Hz rTMS is always inhibitory remains to be fully addressed [54].

Finally, like previous studies assessing adults, adolescents and children with TS, rTMS over SMA has been demonstrated to be safe and well tolerated in most patients. However, one patient complained of severe headaches due to the active rTMS procedure, which deserves attention in future trials.

Limitations

A major limitation of this study is the relatively small size and short blinded phase. A larger sample and longer blinded phase will be needed to evaluate whether or not 6 weeks of low frequency rTMS targeting the SMA is clinically efficacious in reducing tic severity. This is an important consideration given that optimal antidepressant results require 4–6 weeks. One of the major difficulties in running this trial was in recruiting for it, the demands on the patients' schedule were dire and it required a lot of flexibility on the part of the clinical staff. Although we used a rigorous clinical rating method and comprehensive clinical protocol, the results of this study might have been improved by using a patient-specific targeting procedure as recently reported by Wu et al. [23]. Likewise, since cTBS provides more potent inhibitory neuromodulatory effects, the efficacy of fMRI targeted cTBS should be evaluated over a longer period of time in TS patients before any definite conclusions can be made concerning the clinical efficacy of electrophysiological interventions targeting the SMA [36]. In addition, based on our laterality findings and the recent work of Obeso et al. [55], a case can potentially be made to target preferentially the right pre-SMA with cTBS. Specifically, when Obeso combined rTMS with oxygen 15-labeled water ($H_2^{15}O$) positron emission tomography scans acquired during a stop signal task, they found that rTMS-induced changes in excitability of the right pre-SMA (as compared to sham rTMS) enhanced response inhibition. They also found that rTMS over the right pre-SMA was associated with increased blood flow in the left pre-SMA, the left inferior frontal gyrus, as well as the right premotor and right inferior parietal cortex. If rTMS over the right pre-SMA can enhance response inhibition, then it might also have a beneficial effect on tics. Additionally, another

novel means to enhance the potency and duration of inhibitory neuromodulatory effects of 1-Hz TMS is through optimizing the pulse shape, as is done with controllable pulse parameter TMS [56]. We recently reported unidirectional near rectangular pulses are significantly more efficient than conventional cosine bidirectional pulses in inducing inhibitory effects which could be useful in this regard [57].

Another potentially important confounder in this study concerns the inclusion of patients taking psychotropic medications that are known to have an inhibitory effect on brain excitability (e.g. anticonvulsants, benzodiazepines, atypical antipsychotics) [58]. The decision to include these patients was based on our difficulty in recruiting subjects and our wish to have as naturalistic study as possible. However, it is clear that a number of the medications that some of the patients were taking during the course of the trial likely had a direct influence on motor cortical excitability parameters measured by TMS as well as the clinical effectiveness of the intervention.

Conclusion

In the present sham controlled study of SMA-targeted low frequency rTMS, we safely delivered active and sham treatment over 3–6 consecutive weeks for 20 adults with severe TS. On average, during the blinded phase of the study no clinically significant reductions in tic severity were found for the patients receiving active rTMS.

However, our findings of changes in motor cortex excitability measures after 6 weeks of active rTMS suggest that right MT might be a predictor of response to a longer rTMS treatment (i.e., 6 weeks) and that 1-Hz rTMS may be of benefit for some adults with chronic and refractory TS. Future protocols with improved target selection and improved stimulation procedures need to be tested in adults with this disabling condition. In addition, it may be sensible to include subjects with a moderate level of tic severity as well as severe cases, but to exclude subjects on psychotropic medications with the potential to affect cortical excitability. In this way future protocols will avoid the limitations and pitfalls of studies combining TMS with pharmacologic agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a.

Figure 1b.

Figure 1.

Figure 1a. YGTSS Total Tic Score Change from Baseline to Week 3 during Double Blind Phase

Figure 1b. YGTSS Total Tic Score Change from Week 3 to Week 6 during Open Label Phase

Figure 1a and 1b: Figure 1a shows mean Yale Global Tic Severity Scale scores from baseline to week 3 during double blind phase. Figure 1b depicts Yale Global Tic Severity Scale scores from week 3 to week 6 when all patients received active treatment. At the end of 3 weeks (controlled blinded phase) completers showed a reduction of 17.3% with active and 13.2% with sham repetitive transcranial magnetic stimulation (rTMS) in tic severity scores ($p=0.56$). After a 3-week additional active rTMS patients initially randomized for active rTMS showed further improvement. The mean decrease in the YGTSS total tic severity score from Baseline (36.0 [10.2]) to 6 weeks (25.3 [6.7]) for these 7 individuals was significant (10.7 points [29.7%]; $t=2.6$, $df=6$, $p=0.04$).

Table 1

Study (author, year)	Design, population characteristics	Intensity, duration (motor threshold)	Target	Results
Munchau et al., 2002 [15]	Single-blind RCT N=16 TS (7 OCD) (12 males, 38 ± 12.3 yrs)	6 × 20 min sessions (1,200 pulses/d; 1-Hz) - 4 weeks (80% MT)	Motor + premotor cortex	No significant clinical improvement
Chae et al., 2004 [16]	Single-blind RCT; N=8 TS (4 OCD) (5 males, 14.9 ± 16 yrs)	5 × 4-hour-sessions (2,400 pulses/d; 1- or 15-Hz); 5 days (110% MT)	Left motor cortex + left prefrontal cortex	Improvement of tics, OCD and clinical global impression*
Orth et al., 2005 [17]	Single blind (crossover) RCT; N=5 Non-OCD TS (4 males, mean age 29 yrs)	Two-day protocols, crossover each 4 weeks (1,800 pulses/d; 1-Hz) (80% MT)	1 Left pre-motor + right premotor cortex; 2 Left premotor + sham right premotor; 3 Sham right + sham left premotor cortex	No significant clinical improvement
Mantovani et al., 2006 [18]	Open Label N=10 (5 OCD, 3 TS, 3 OCD +TS) (8 males, 33.5 ± 13.5 yrs)	10 × 20 min sessions (1,200 pulses/d; 1-Hz); 2 weeks (100% MT)	SMA (bilateral)	Improvement of tics, OCD and clinical global impression*
Mantovani et al., 2007 [19]	Open label; N=2 TS (male, 16 and 22 yrs)	8 to 10 × 20 min sessions (1,200 pulses/d; 1-Hz); 2 weeks (110% MT)	SMA (bilateral)	Improvement of TS and OCD*
Kwon et al., 2011 [20]	Open Label; N=10 male TS children (11.2 ± 2.0 yrs)	10 × 20 min-sessions (1,200 pulses/d; 1-Hz); 2 weeks (100% MT)	SMA (bilateral)	Improvement of tics and clinical global impression*
Le et al., 2013 [21]	Open Label; N=25 TS + comorbidities (22 males, mean 10.6 ± 2.2 yrs)	20 × 20 min sessions (1,200 pulses/d; 1-Hz); 4 weeks (110% MT)	SMA (bilateral)	Improvement of tics, ADHD, depressive and anxiety symptoms*

ADHD: attention deficit hyperactivity disorder; OCD: obsessive-compulsive disorder, TS: Tourette syndrome; MT: motor threshold; SMA: supplementary motor area

* $p < .05$

Table 2

Demographic and clinical characteristics

	Active rTMS	Sham	<i>p</i>
Sample size	9	11	NS
Right-handed	9	7	NS
Female/Male	2/7	2/9	NS
Age (mean $\pm$ S.D.)	29.1 (7.4)	37.5 (14.2)	NS
Age of onset	6.2 (2.6)	8.0 (5.1)	NS
Duration of illness	22.9 (8.3)	34.7 (12.9)	NS
Co-morbid OCD	3	2	NS
Co-morbid ADHD	5	3	NS
Baseline YGTSS	35.8 (9.2)	36.3 (8.2)	NS
Baseline PUTS	25.5 (6.5)	29.0 (5.6)	NS
Baseline CGI - Severity	4.9 (0.8)	5.4 (0.8)	NS
Baseline Y-BOCS	12.1 (9.5)	8.2 (10.2)	NS
Baseline ASRS	27.5 (12.8)	21.5 (10.5)	NS
Baseline HAM-D-24	10.8 (7.3)	9.4 (7.1)	NS
Baseline HAM-A-14	7.2 (5.8)	6.3 (4.0)	NS
Alpha -2 agonists	1	3	
Neuroleptics	2	2	
SRI or SSRI	2	2	
Benzodiazepines	2	2	
Anticonvulsants	1	2	

rTMS, Repetitive transcranial magnetic stimulation; OCD, Obsessive-compulsive disorder; ADHD, Attention Deficit Hyperactivity Disorder; YGTSS, Yale Global Tic Severity Scale [25]; PUTS, Premonitory Urge Tic Scale [28]; CGI, Clinical Global Impression Severity scale [24]; YBOCS, Yale–Brown Obsessive Compulsive Scale [31]; ASRS, ADHD Self Rating Scale [32]; HAMD-24, Hamilton Depression Rating Scale – 24-item [26]; HAMA-14, Hamilton Anxiety Rating Scale – 14-item [34]; Alpha-2 agonists (clonidine, guanfacine); Neuroleptics (haloperidol, risperidone, quetiapine), SRI (clomipramine), SSRI (fluoxetine, paroxetine), Anticonvulsants (lamotrigine, valproic acid, oxcarbazepine); NS: $p > .05$.

Table 3
Clinical Measures across 3-week active and sham rTMS in 20 patients with Tourette syndrome

Dependent measures	Active rTMS (n = 9)				Sham rTMS (n = 11)				MMRMA
	Baseline	Week 1	Week 2	Week 3	Baseline	Week 1	Week 2	Week 3	
YGTSS	35.8 (9.2)	28.1 (10.4)	30.3 (9.0)	29.6 (11.9)	36.3 (8.2)	34.5 (8.7)	33.2 (9.0)	31.5 (8.1)	NS
PUTS	25.5 (6.5)	23.1 (7.3)	24.9 (6.9)	24.6 (6.0)	29.0 (5.6)	27.2 (5.3)	28.5 (4.7)	28.7 (5.3)	NS
CGI - Severity	4.9 (0.8)	4.7 (0.9)	4.6 (1.3)	4.6 (1.1)	5.4 (0.8)	5.1 (0.9)	4.8 (1.0)	4.4 (1.0)	NS
Y-BOCS	12.1 (9.5)	6.3 (6.5)	8.4 (8.3)	7.0 (7.9)	8.2 (10.2)	6.1 (10.2)	5.4 (9.9)	4.8 (7.8)	NS
ASRS	27.5 (12.8)	23.6 (13.2)	29.4 (16.9)	25.1 (12.3)	21.5 (10.5)	20.8 (15.2)	20.5 (14.1)	19.1 (13.0)	NS

rTMS, Repetitive transcranial magnetic stimulation; OCD, Obsessive-compulsive disorder; ADHD, Attention Deficit Hyperactivity Disorder; YGTSS, Yale Global Tic Severity Scale; PUTS, Premonitory Urge Tic Scale; CGI, Clinical Global Impression Severity scale; YBOCS, Yale-Brown Obsessive Compulsive Scale; ASRS, ADHD Self Rating Scale; MMRMA, Mixed model repeated measures analysis with baseline scores as a covariate; NS: $p > .05$.

Resting motor thresholds across 3-week active and sham rTMS in patients with Tourette syndrome[‡]

Table 4

Motor Threshold (MT)	Active rTMS (n=8)		Sham rTMS (n=10)	
	Baseline	Week 3	Baseline	Week 3
Right MT* Mean (SD)	68.0 (11.5)	63.5 (10.3)	61.0 (11.2)	61.6 (12.0)
Left MT Mean (SD)	63.5 (10.9)	61.8 (10.4)	66.4 (13.3)	65.0 (13.1)

rTMS, Repetitive transcranial magnetic stimulation; Resting motor threshold (MT) was defined as the minimum magnetic flux needed to elicit a threshold EMG response (50 μ V in peak-to-peak amplitude) in a resting right or left target muscle (*abductor pollicis brevis*).

[‡] Data are included only for those patients that completed phase 1 of the study (n = 18).

* There was a significant difference between Active treatment and Sham in change in Right MT from Baseline to Week 3: $t=2.32$, $df=16$, $p=0.034$.

Data are also available for 6 of the 7 patients who received Active rTMS for 6 weeks. Their right MT (mean [SD]) went from 63.3 (14.1) at Baseline to 56.7 (12.7) at 3 weeks and to 58.0 (9.3) at 6 weeks ($t=2.4$, $df=5$, $p=0.06$). No differences in the left TM were observed over the 6 week interval (data not shown).