Deep-TMS Add-On Treatment for Intractable Tourette syndrome: A Feasibility Study

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Deep-TMS Add-On Treatment for Intractable Tourette syndrome: A Feasibility Study

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Deep-TMS for Intractable Tourette Syndrome

Abstract

Objectives: In a considerable minority of patients who suffer from Tourette syndrome (TS) the disorder persists into adulthood and is associated with severe symptoms and limited therapeutic options. Repetitive transcranial magnetic stimulation (rTMS) to the supplementary motor area (SMA) has shown promising therapeutic results. Deep rTMS is a novel technology that enables deeper non-invasive cortical stimulation. This open label pilot study is the first to examine the possible role of deep rTMS as add-on treatment for intractable TS.

Methods: Twelve patients were recruited in order to examine bilateral SMA inhibition via deep-TMS using the HBDL coil, as a possible treatment for adult TS treatment-resistant patients. Two patients did not complete the 20 day study protocol.

Results: There were no significant side effects. While tics did not improve among the group as a whole, the subgroup of six patients with combined TS and OCD (obsessive compulsive syndrome) showed significant improvement in tic severity (p=.037).

Conclusions: These findings support the safety of deep rTMS for treating TS. The results also highlight the importance of studying the different TS syndromes separately (e.g., with or without OCD comorbidity) when evaluating deep rTMS protocols for TS patients.

Introduction

Tourette syndrome (TS) is a childhood onset disorder typified by the continuous presence of both motor and vocal tics. Tics are sudden, rapid, stereotyped, repetitive, non-rhythmic movements or vocalizations affecting discrete muscle groups, usually preceded by a sensory *component* (Cavanna and Seri, 2013). This eventually results in the performance of movements or sounds. Although symptoms typically subside by early adulthood, a significant number of patients continue to experience severe symptoms across their lifespan and some (around 10 %) experience even worse symptoms during adulthood (Bloch et al., 2011, Hassan and Cavanna, 2012). Cases of tics that persist are usually associated with severe symptoms and burden (Cavanna et al., 2012, Hassan and Cavanna, 2012, Robertson, 2012). Possible interventions include cognitive behavioral therapy, pharmacotherapy and deep brain stimulation (Parraga et al., 2010, Eddy et al., 2011, Robertson 2012, Cavanna and Seri, 2013). These therapies are highly effective for roughly 30-40% of treated patients. However, pharmacotherapy mainly includes antipsychotics and alpha 2 blockers, which can produce agonizing side effects, and DBS is invasive and carries risks related to brain surgery (Conca et al., 2011, Muller-Vahl et al., 2011, Roessner et al., 2011, Verdellen et al., 2011, Dutta and Cavanna, 2013, Plessen, 2013, Roessner et al., 2013).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has been used for the treatment of a variety of brain disorders. rTMS uses brief, intense pulses of electric current delivered to a coil placed on the subject's head to generate an electric field in the brain via electromagnetic induction. The induced electric field modulates the neural transmembrane potentials and, thereby, neural activity. The effect is determined by the

intensity, frequency, and number of pulses used; the duration of the course; the coil location and, possibly, the type of coil used. In general, high-frequency (>5 Hz) rTMS promotes cortical excitability, while low-frequency (⩽1 Hz) rTMS inhibits cortical excitability (Rossi et al., 2009, Di Lazzaro et al., 2011, Le et al., 2013). Recent rTMS for tic disorder studies have targeted the supplementary motor area (SMA). The SMA modulates connections between motor circuits the limbic system and cognitive processes. (Munchau et al., 2002, Orth et al., 2005, Snijders et al., 2005, Mantovani et al., 2006, Le et al., 2013). Recent imaging studies have revealed increased connectivity between the SMA and the motor cortex in patients suffering from chronic tic disorders as opposed to controls. Functional MRI (fMRI) studies have found that the SMA appears to be overactive in TS patients when they are performing motor tasks; they have also found that the bilateral SMAs are the most active regions immediately before tic execution(Franzkowiak et al., 2012, Eichele and Plessen, 2013, Neuner et al., 2013). The need to apply inhibitory stimulation to the SMA has been supported by a recent study that showed that echophenomena (the mimicking of another person, a behavior related to TS) can be induced by excitatory rTMS over the SMA in healthy adults (Finis et al., 2013). While the earlier well-conducted protocols demonstrated no beneficial effect when using an intensity of 80% of the motor threshold (Munchau et al., 2002, Orth et al., 2005), recent studies using a higher intensity and number of treatment days showed promising results in both adults (Mantovani et al., 2007) (Mantovani et al., 2006) and children (Kwon et al., 2011, Le et al., 2013). The magnetic fields of standard rTMS devices extend into the cortex only one to two centimeters from the surface. This is a possible limitation in the efficacy of rTMS.

Deep-TMS is a modification of standard TMS that enables deeper non-invasive cortical stimulation at a depth of 3 cm (Zangen et al., 2005). In treatment-resistant depression, rTMS stimulation targets the prefrontal cortex, and evidence is accumulating for an advantage of the deep rTMS H coils over the usual coils (Minichino et al., 2012), pointing to the possibility that even with alleged superficial brain structures deeper modulation is advantageous.Deep-TMS is FDA approved for the treatment of drug-resistant major depressive disorder (MDD) and has gained worldwide attention as a possible therapeutic tool for various neurological conditions (Bersani et al., 2013).

The current preliminary study is the first to examine bilateral SMA inhibition via HBDL coil, which is a type of the H deep-TMS coil, as a possible treatment for adult TS treatment-resistant patients.

Methods

Participants

Recruitment was done via psychiatric and neurological clinics in the district tertiary Tourette clinics, and advertisements.

Main inclusion criteria included: needing to be between the ages of 18 and 65; suffering from TS, which assessment was determined by a senior psychiatrist according to the structured clinical interview for DSM-IV; experiencing considerable current tic severity (Yale Global Tic Severity rating Scale (YTSS) > 20) that persisted for at least four months; showing a lack of response to or intolerance for at least two full trials of anti-tic pharmacotherapy; undergoing no change in pharmacotherapy one month prior to admission. Since Tourette syndrome usually

coexists with behavioral problems – i.e., approximately 90% of Tourette patients have comorbid conditions such as ADHD, OCD, anxiety and self-injurious behaviors (Robertson, 2000) – common comorbidities were not an exclusion.

Main exclusion criteria included: presence of any other neurological or severe general medical conditions; substance abuse in the past year; schizophrenia spectrum disorders; bipolar disorder; current major depressive episode; mental retardation; high suicidal risk; any known contraindication to TMS, use of a dosage above haloperidol 7.5mg/d, or its equivalent.

The study was approved by the national IRB. All patients agreed to participate in the study and signed the informed consent form.

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Procedure

Motor threshold (MT) was defined as the lowest stimulation intensity capable of producing motor-evoked potentials of the right abductor pollicis-brevis in 50% of the trials performed. As in previous rTMS studies aimed at treating TS, the vertex (Cz) of each subject was measured in order to assure proper coil placement, and the SMA was defined as 15% of the distance between inion and nasion anterior to Cz on the sagittal midline. (Mantovani et al., 2006, Le et al., 2013). Daily deep-TMS sessions were conducted for four consecutive weeks. Each session consisted of four 1HZ trains (5 minutes per train; 2 minutes inter-train interval) at an intensity of 110% of the measured MT, for a total of 1200 magnetic pulses per session.

Clinical evaluations were performed at baseline, at the end of the treatment period (four weeks).

Study device

rTMS sessions were conducted using a Magstim Super Rapid stimulator (Magstim, UK) with the novel deep-TMS HBDL-coil. The HBDL coil targets the prefrontal orbitofrontal cortex and the SMA.

Clinical evaluations

The primary outcome measure was the Yale Global Tic Severity rating Scale (YTSS). Secondary outcome measures were: Yale-Brown Obsessive Compulsive Disorder Scale (YBOCS), Clinical Global Impression (CGI), Social Adaptation Self-evaluation Scale (SASS), Hamilton Depression Rating Scale (HDRS-21), Hamilton Anxiety Rating Scale (HARS-14), quick inventory of depressive symptomatology self-report (QIDSSR).

Results

The study sample consisted of 12 patients (50% male) with an age range of 20 to 61 years (mean=32.6, SD=12.7). Seven patients had never been married. At the time of the study, six of the patients were working on a part-time basis, three were holding down professional jobs, and four were not employed. All of the patients felt that their lives were severely affected by their tic disorders. Six patients suffered from current comorbid OCD (two in the mild severity range, two in the moderate range, and two in the severe-extreme severity range), and four suffered from ADHD. Ten of the patients had been taking multiple medications for many years, beginning this regimen before the age of 10, in order to treat their tics. Two patients started pharmacotherapy as adults. Eleven patients received more than five unsuccessful trials of medications to treat their tics from at least two classes. At the time of the study two patients were not taking any medications; the other ten were taking varied combinations of SSRI's (six patients),

antipsychotics (three patients), Clonidine (three patients), benzodiazepines (two patients), Lamotrigen, Reboxetine, Mirtazepine, Amitriptaline (one patient each). Two patients did not complete the study (one stopped after seven treatment days, and one after 13); both felt they were not sufficiently helped by the treatment to continue coming, and they found attending the sessions too difficult. Data was analyzed on an intention-to-treat basis, with the last evaluation carried forward (LOCF) for patients dropping out of the study. Analyses were conducted using the Statistical Package for Social Sciences (SPSS), Version 16.

A repeated measures analysis of variance (ANOVA) with a within-subjects factor of treatment [baseline, mid-point (visit 10) and post treatment (visit 20)] was conducted to determine differences in the primary outcome measure (tics as measured by the YTSS) before and after treatment. The ANOVA was not significant [$F(2)=1.26$, $p=0.302$]. A similar ANOVA was conducted for OCD symptoms as measured by the YBOCS (secondary outcome measure). The analysis approached significance [$F(1.3)=3.95$, $p=0.056$]; a trend towards an improvement was found for the OCD symptoms. Descriptive data and statistical analyses comparing tic and OCD symptoms before and after rTMS are presented in Table 1.

Significant improvement was ~~also~~ found in a secondary measure of the study: i.e., level of depression (HDRS-21) [$F(2)=4.47$, p=0.029]. Post-hoc analyses revealed significant differences between baseline and mid-point treatment (visit 10) [$F(1)=8.89$, p=0.018]. However, it should be noted that the baseline severity of depression was below the clinical cutoff-point (HDRS-21: mean=4.9). Thus, the clinical relevance of this finding is questionable. In addition, repeated measures ANOVA were found to be significant in the clinical global impression [CGI; $F(2)=8.53$, p=0.005]. However, subsequent analyses have not found significant differences

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between any of the paired assessment points, and all other analyses were non-significant. No side effects were reported apart from an uncomfortable sensation on the scalp (two patients) and mild headaches (three patients).

An exploratory analysis was performed among the subgroup of patients who had suffered from comorbid TS and OCD (n=6). The repeated measures analysis revealed a significant improvement in tics [YTSS: $F(2)=4.65$, $p=0.037$]. Post-hoc analyses indicated significant differences between baseline (mean=73.33, SD=23.90) and mid-point treatment (mean=66.50, SD=25.39) [$F(1)=10.87$, $p=0.022$]. Moreover, a significant improvement was also found in OCD symptoms [YBOCS: $F(2)=5.47$, $p=0.025$]. Subsequent analyses found significant differences between baseline (mean=23.00, SD=11.10) and mid-point treatment (mean=17.60, SD=8.86) [$F(1)=8.25$, $p=0.035$]. No significant correlation was found between OCD severity change and tic severity change (pre-post treatment) in this subgroup [$r(p)=0.73$, $p=0.101$].

Discussion:

The current preliminary study is the first to examine bilateral SMA inhibition via deep-TMS, as a possible add-on treatment for adults suffering from treatment-resistant Tourette syndrome. No severe side effects were reported.

When analyzing the entire group of subjects, no difference was found in tic severity following the treatment. A trend towards significant improvement was found, however, in OCD symptoms.

Dividing the group into those who suffered from OCD comorbidity, and those without OCD comorbidity, a significant improvement in tic severity (p=0.037) in patients with OCD

comorbidity was revealed. In this subgroup, improvement in OCD symptoms was also significant (p=0.025).In recent years evidence to support differences between TS syndromes according to comorbidities has been accumulating. Clinically, psychiatric comorbidity including OCD but also ADHD and depression are risk factors for a worse prognosis and demand a more complex treatment plan (Jalenques et al., 2012). Studies of the genetics of TS differentiate between "subphenotypes" of TS and support a strong genetic role for the combined TS, OCD, ADHD syndrome as opposed to the other TS "subphenotypes" (Grados et al., 2008). In addition, recent functional imaging studies support the role of unique networks in the TS OCD syndrome as opposed to TS alone syndrome (Pourfar et al., 2011). In the DSM 5, tics are a specifier in the diagnosis of OCD. From a phenomenological perspective, there are some similarities between tics and obsessions. Both have a sensory component: the primordial urge of TS and the unease that precedes the compulsion. The difference seems to lie in how aware the individual is of the motor act , and how much control he/she has over the act. The possibility that this difference is a reflection of different networks involved, based on more intrinsic stimuli in TS as opposed to OCD, has been hypothesized and points to a possible explanation for the difference in response between the TS-only and the TS-combined-with-OCD patients in the presented study (Ganos et al., 2013). It should be noted that other studies of rTMS for the treatment of TS have raised the possibility that treatment is effective for the combined TS OCD syndrome but not for all TS patients (Greenberg et al., 2000).

This feasibility study suggests that deep-TMS, in which the HBDL coil is directed at the SMA, is not useful for TS in general but improves tic symptoms in patients suffering from Tourette syndrome co-morbid with OCD. The trend towards improvement in OCD symptoms can be seen

as additional support for the effect on the TS OCD syndrome. The lack of treatment effect on TS patients free from OCD comorbidity may assist in the future identification of the TS population responsive to inhibition of the SMA A potential discriminative effect of rTMS joins the phenotypic difference, the genetic findings and the findings from functional brain imaging to construct a better understanding of the pathophysiology of TS. It is important to bear in mind the broad spectrum of therapeutic possibilities contained within magnetic stimulation. TMS enables us to tailor therapy for the individual by using different locations in the brain according to different disease markers. It is possible that TS alone would demand a different coil location. One possibility for future targeting of the deeper penetrating coil is to target the basal ganglia in those patients not responsive to modulation of the SMA.

The study's limitations include being an open-label small sample, conducted among a population of severely ill patients. In future, larger, double-blind, placebo-controlled studies, it would probably be worthwhile to use different rTMS treatment protocols according to TS comorbidities. In addition, the need to study the comorbidities, specifically OCD using the same rTMS protocols, would likely shed light on the specificity of different pathologies. This pilot open-labeled study raises the possible efficacy of bilateral SMA inhibition using the deep HBDL coil to treat resistant patients suffering from TS comorbid with OCD.

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Conflict of interest:

Professor Levkovitz has financial interests in Brainsway, Inc. Dr. Arad and Dr. Bloch do not have any conflict of interest in the conduct and reporting of this research.

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Table 1:

Comparison of tic and OCD symptoms before and after rTMS

Patient	YBOX[1]	YBOX[2]	YGTSS[1]	YGTSS[2]
1	18	7	44	29
2	35	15	95	80
3	13	4	72	61
4	38	35	99	100
5	22	22	64	64
6	12	11	77	67
7	2	0	26	49
8	0	0	43	34
9	0	0	54	46
10	0	0	73	70
11	0	0	43	57
12	0	0	87	84
Mean	11.77	7.75	64.75	61.75
SD	14.02	11.00	23.06	20.60
t-test	2.14		0.90	
p-value	0.05		0.38	

Notes:

OCD: Obsessive Compulsive Disorder; rTMS: Repetitive Transcranial Stimulation; YBOCS: Yale-Brown Obsessive Compulsive Disorder Scale; YGTSS: Yale Global Tic Severity rating Scale.

1 Before rTMS
2 At the end of rTMS course