

Subthreshold rTMS over pre-motor cortex has no effect on tics in patients with Gilles de la Tourette syndrome

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Abstract

Objective: A previous study showed no effect of 1 Hz repetitive transcranial magnetic stimulation (rTMS) on tics in Gilles de la Tourette Syndrome (GTS). We modified the rTMS protocol in order to investigate some of the possible methodological reasons for the negative outcome in that study.

Methods: In a single blinded placebo-controlled cross-over study in five GTS patients without obsessive compulsive disorder we probed whether longer trains (1800 stimuli) of 1 Hz pre-motor cortex rTMS at 80% of active motor threshold and application to both hemispheres can improve tics in GTS. This was measured with the Yale Global Tic severity rating scale, the MOVES self-rating scale and video analysis.

Results: We found no significant effect of either left pre-motor cortex stimulation alone, or left pre-motor followed by right pre-motor cortex stimulation.

Conclusions: These results suggest that the rTMS protocol used in this study is not useful for the treatment of tics in GTS.

Significance: rTMS protocols need to be modified substantially in order to explore their potential for the treatment of tics in GTS.

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1. Introduction

Gilles de la Tourette syndrome is a childhood-onset neuropsychiatric developmental disorder characterised by motor and phonic tics. Comorbidity is very common, in particular obsessive compulsive disorder (OCD) and

attention deficit hyperactivity disorder (ADHD) (Freeman et al., 2000; Leckman, 2002; Robertson, 2000). Pharmacological treatment of tics may come at the price of marked side effects and is not always helpful (Leckman, 2002; Robertson, 2000) so that alternative treatments for tics need to be explored.

The pathophysiology of GTS remains unclear. Neurophysiological evidence suggests that the motor cortex is hyperexcitable in GTS patients (Ziemann et al., 1997). Imaging studies revealed that during tic suppression and tics, metabolism was increased in pre-motor, pre-frontal and motor cortex indicating increased activity in these brain areas (Eidelberg et al., 1997; Peterson et al., 1998; Stern et al., 2000). This suggests the involvement of loops

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connecting basal ganglia, pre-motor, motor and sensory cortex, thalamus and possibly other brain areas in GTS thus compromising the ability of patients to suppress unwanted behaviours (Leckman, 2002).

Low frequency repetitive transcranial magnetic stimulation (rTMS) is known to have inhibitory effects on the stimulated brain area (Chen et al., 1997), and, recently, 1 Hz rTMS at 80% AMT applied to the pre-motor cortex had an inhibitory behavioural effect in healthy individuals (Schlaghecken et al., 2003). Thus, in a previous study, Munchau et al. (2002) hypothesised that such an rTMS protocol might normalise motor or pre-motor cortical excitability in GTS translating into the improvement of tics. However, 1200 stimuli of 1 Hz left pre-motor or motor cortex rTMS at 80% AMT were ineffective. Most patients in that study had another diagnosis in addition to GTS, and it is therefore possible that the patient group was too heterogeneous (Munchau et al., 2002). This could be relevant because GTS patients without OCD have been shown to differ from those with OCD electrophysiologically and pharmacologically (Cath et al., 2001; Greenberg et al., 2000; Ziemann et al., 1997). In addition, we tested whether the effect of rTMS on tics might have been missed in the Munchau et al. (2002) study as the outcome relied on self-report tic rating scales alone.

Therefore, in the present single blinded placebo-controlled cross-over study, only GTS patients without co-morbid OCD were included; the number of stimuli was increased to 1800 and applied to the pre-motor cortex of both hemispheres in turn, and the assessment of the effect of rTMS on tics included videotape analysis and the Yale Global Tic Severity Scale (YGTSS), a clinician-rated tic scale.

2. Material and methods

2.1. Patients

Five patients with a DSM-IV diagnosis of GTS were studied (4 men, median age 29, range 19–52). Two patients had a DSM-IV diagnosis of ADHD. None of the patients had OCD according to DSM-IV criteria. Three patients were on neuroleptics (haloperidol, risperidone, pimozide) and one patient was on fluoxetine. All patients remained on their respective drug treatment throughout the study. All patients were TMS naïve.

Patients gave informed written consent, and the Joint Ethics Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery approved the study protocol.

2.2. Transcranial magnetic stimulation

Patients were seated in a comfortable chair. They were asked to relax as much as possible but not to suppress their

tics. The experimental set-up for TMS was as described previously (Orth et al., 2003). In brief, active (AMT) and resting motor thresholds (RMT) were determined before and after each rTMS train over the motor cortex hand area (first dorsal interosseus, FDI) hot spot in both hemispheres. RMT, or AMT, were defined as the minimum intensity needed to evoke an MEP of > 50 or 200 μ V, respectively, amplitude in at least 50% of trials in the relaxed, or tonically active, respectively, FDI. First, thresholds were approached from above threshold in steps of 1% stimulator output. When no MEP could be elicited the intensity was increased in 1% stimulator output steps until, at threshold, a minimal MEP was observed. The coil position for pre-motor rTMS was defined as 3 cm anterior to the FDI hot spot in the M1 area of the motor cortex, a relationship supported by correspondence studies in monkeys and functional imaging studies in humans (Picard and Strick, 2001). rTMS was applied using a Magstim Rapid (Magstim Co., Whitland, Dyfed, UK), which generates a biphasic (posterior–anterior/anterior–posterior) current flow in the brain. For sham stimulation, a Nostim coil giving an acoustic artefact was used (Magstim Co.). All the stimulation variables followed the published safety guidelines (Wassermann, 1998).

Three different rTMS protocols (1800 stimuli, 1 Hz, 80% AMT) were evaluated in pseudo-random order with the patient blinded to the respective condition.

Protocol A. Left pre-motor cortex followed by right pre-motor rTMS.

Protocol B. Left pre-motor cortex rTMS followed by sham stimulation of the right pre-motor cortex.

Protocol C. Sham stimulation of left pre-motor cortex followed by sham stimulation of right pre-motor cortex.

Each of the protocols was repeated at the same time on the following day; there was an interval of 4 weeks between different protocols.

2.3. Assessment of tics and data analysis

Before the first and after the second day of each of the rTMS protocols, tic severity was measured using the clinician-rated Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989), and the Motor and Vocal tic Evaluation Survey (MOVES) self-rating scale (Gaffney et al., 2002). Before each intervention, the YGTSS and the MOVES assessed tic severity over the preceding week. In contrast, the YGTSS and MOVES after the second day of the intervention measured tic severity on those 2 days alone. For the YGTSS, a global score, a motor tic and a vocal tic subscore were calculated. For the MOVES, a total score and a tic subscore were differentiated. In addition, patients were videotaped as described by Goetz et al. (1987). An examiner who was blinded to the rTMS protocol and did not know the patients counted the total number of motor and vocal tics per

Table 1
Effect of rTMS on rating scale scores

	L+R pre-motor		L pre-motor		Sham	
	Before	After	Before	After	Before	After
MOVES total	11.8 (5)	11.2 (4.7)	13.4 (4.7)	11 (5.1)	11.8 (4.1)	9.2 (3.1)
MOVES tic	7.4 (2.3)	7.8 (2.6)	8.2 (1.3)	7.2 (2.6)	7.2 (1.3)	6.2 (1.5)
YGTSS total	46.2 (11)	45 (8.3)	51 (27.3)	51.2 (27.4)	48.2 (8.0)	49.4 (8.8)
YGTSS motor	14.4 (2.7)	13.4 (1.9)	15.2 (4.5)	15.2 (4.9)	13.8 (2.6)	14.4 (3.5)
YGTSS vocal	7.8 (3.2)	7.4 (2.6)	9.8 (4.8)	10 (4.7)	8.4 (6)	9 (5.5)

The results were similar with no effect of any of the rTMS protocols. The data represent means (SD) of five patients. L+R, left pre-motor followed by right pre-motor rTMS; L, left pre-motor followed by sham right pre-motor rTMS; Sham, sham stimulation; MOVES, Motor and Vocal tic evaluation survey; YGTSS, Yale Global Tic Severity Scale.

minute. Tics were rated using the Modified Rush Video Scale (MRVS) (Goetz et al., 1999).

Differences of AMT, or RMT, between sessions was analysed using a repeated measures ANOVA. In order to assess the effect of rTMS on AMT, RMT or tic severity, we asked whether data before each protocol was different to the data after the second day of each of the rTMS protocols. This was tested using a repeated measures ANOVA with AMT, RMT or the tic assessment (MOVES scores, YGTSS, each of the video scores) as independent variable and time (before or after rTMS) and rTMS protocol as the within-subject factors.

Mauchley's test examined for sphericity. A P value <0.05 was considered significant. A significant main effect in the ANOVA was followed by post hoc paired t test analysis. The Greenhouse-Geisser correction was used for non-spherical data.

3. Results

3.1. Transcranial magnetic stimulation

Patients had a mean AMT of 43% of stimulator output (SD 7.9, range 31–54) on the left motor cortex, and a mean of

43% (SD 8.5, range 30–58) on the right motor cortex. Mean RMT was 53% (SD 8.9, range 39–62) on the left and 53% (SD 9.3, range 39–63) on the right motor cortex, respectively. Irrespective of the protocol, rTMS did not have a significant effect on AMT or RMT of the same or the contralateral motor cortex. In each patient, AMT was similar between protocols ($P > 0.05$).

3.2. The effect of rTMS on tic severity

rTMS had no significant effect on global tic severity either assessed by the clinician-rated YGTSS, video analysis or as judged by the patients (MOVES), irrespective of which rTMS protocol was used ($P > 0.05$ for all analyses, Table 1). This was also true when analysing individual subscores that assess motor or vocal tics alone irrespective of whether this was clinician-rated, self-rated, or based on the video analysis using raw tic counts per minute, or the MRVS ($P > 0.05$ for all analyses, Table 2).

4. Discussion

In the present single blinded, placebo-controlled cross-over study, we did not find an effect of pre-motor 1 Hz

Table 2
Video analysis of tic severity

	L+R pre-motor		L pre-motor		Sham	
	Before	After	Before	After	Before	After
Motor tic count/min	15 (16.9)	10.2 (8.5)	9.8 (5.1)	10.2 (5.3)	14.4 (17.2)	7.6 (6.5)
Vocal tic count/min	4.1 (3.3)	4.2 (2.6)	4.2 (3.7)	2.5 (3.2)	2.5 (2.8)	3.2 (3.2)
MRVS total	8.9 (5.5)	8 (5.3)	9.6 (4.1)	8 (3.7)	9.2 (4.1)	8.6 (4.3)
MRVS 1	2.4 (0.9)	2 (1.2)	2.2 (0.4)	2 (0.7)	2 (1.2)	2.2 (1.1)
MRVS 2	0.8 (0.4)	0.6 (0.5)	1 (0)	1 (0)	1.4 (0.9)	0.8 (0.4)
MRVS 3	1.5 (1.1)	1.4 (0.9)	1 (1)	0.6 (0.9)	0.8 (0.8)	1 (1)
MRVS 4	2.4 (1.8)	2.4 (1.8)	3 (1.2)	2.8 (1.3)	3 (1.2)	2.8 (1.3)
MRVS 5	1.8 (2)	1.6 (1.8)	2.4 (1.5)	1.6 (1.5)	2 (1.9)	1.8 (1.6)

There was no significant difference between tic severity measured before and after each of the three different rTMS protocols. Data are means (SD) of five patients. L+R, left pre-motor followed by right pre-motor rTMS; L, left pre-motor followed by sham right pre-motor rTMS; Sham, sham stimulation; MRVS, modified Rush video scale; MRVS 1, number of body areas involved with tics; MRVS 2, motor tic severity; MRVS 3, phonic tic severity; MRVS 4, frequency of motor tics; MRVS 5, frequency of phonic tics; MRVS total, sum of the five domain scores; AYSV, adapted Yale video scale.

rTMS at 80% AMT on the severity of tics in GTS. This is in accord with the results of a previous study, even though we modified the rTMS protocol in order to investigate some of the possible methodological reasons for the negative outcome in that study (Munchau et al., 2002). Previously, the outcome (tic severity) was measured using a self-rating scale alone (Munchau et al., 2002). As tics are difficult to measure it is possible that changes of tic severity following rTMS might thus have escaped detection. Therefore, in the present study we employed two clinician-rated instruments (YGTSS and video analysis) and one self-rating scale, the MOVES. The results obtained with these instruments were concordant in showing no effect of rTMS. Thus, we think it is unlikely that an effect of rTMS on tic severity was missed.

It has been suggested that patients with GTS share similarities with but also differ from patients with OCD electrophysiologically and pharmacologically (Cath et al., 2001; Greenberg et al., 2000; Ziemann et al., 1997). We therefore only included patients without a diagnosis of OCD. Nonetheless, our results do not support the hypothesis that GTS patients without concomitant OCD do better with our rTMS protocol compared with those patients with both diagnoses. The number of patients in our study was small, though. This means that we cannot comfortably extrapolate from our data to the wider population of GTS patients, and it is possible that some GTS patients may benefit from rTMS. However, our patients were representative for the majority of patients in our specialist clinic. If our rTMS protocol were clinically meaningful for tic treatment we would have expected at least some effect in our patients. We felt that the lack of any indication for a response to our rTMS protocol did not warrant the study of more patients in particular as the protocol was very time consuming and required numerous visits by the patients.

Finally, we may not have chosen the right rTMS protocol. We extended the number of stimuli applied to the pre-motor cortex from 1200 to 1800 on each of the two consecutive days, and we compared left pre-motor cortex stimulation alone with left pre-motor cortex stimulation followed by right pre-motor cortex stimulation. This tested whether in the previous study (Munchau et al., 2002) either the rTMS trains were too short or rTMS might have to be given to both cerebral hemispheres. Another possible explanation for the negative results in both the present and the previous study may be that the stimulation intensity was too low. rTMS with an intensity of 80% AMT was shown to have an inhibitory effect upon behaviour in healthy subjects (Schlaghecken et al., 2003). These behavioural effects in healthy individuals may, however, not translate into a clinical effect, i.e. an improvement of tics, in GTS patients. In patients with other movement disorders higher stimulation intensities (90% RMT) were used to produce a clinical effect either using the same rTMS frequency of 1 Hz (Siebner et al., 1999a) or 5 Hz (Siebner et al., 1999b).

In conclusion, our results do not support a role for pre-motor rTMS at 1 Hz and 80% AMT in the treatment of tics

in GTS. The evaluation of effects on tics of different rTMS protocols, e.g. using higher intensities of stimulation, larger numbers of stimuli given over more than 2 days, or different stimulation sites, needs to be the subject of future studies.

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