

The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder.

A randomized, double blind, sham controlled study.

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Abstract

BACKGROUND: The goal of our study is to assess whether transcranial magnetic stimulation (rTMS) would facilitate the effect of antidepressant in OCD patients.

METHOD: The aim of the randomized, double-blind, sham controlled study was to compare the 2 and 4 week efficacy of the 10 sessions rTMS with sham rTMS in serotonin reuptake inhibitor resistant OCD patient. Thirty three right-handed patients were randomly assigned to either active rTMS or to sham rTMS. Active rTMS with the frequency of 1 Hz at 110% of motor threshold (MT) was administered over the left dorso-lateral prefrontal cortex. The same time schedule was used for sham administration. Thirty patients finished the study, three patients' dropped out at the beginning. Psychopathology was assessed by CGI, HAMA, Y-BOCS and BAI before the treatment, immediately after the experimental treatment, and 2 weeks after the experimental treatment by an independent reviewer.

RESULTS: Both groups improved during the study period but the treatment effect did not differ between them in any of the instruments.

CONCLUSION: Low frequency rTMS administered over the left dorso-lateral prefrontal cortex during 10 daily sessions did not differ from sham rTMS in facilitating the effect of serotonin reuptake inhibitors in OCD patients.

Introduction

Systematic research over the past two decades has demonstrated that obsessive compulsive disorder (OCD) is associated with dysfunction of the cortico-striato-thalamo-cortical circuitry, particularly in the orbitofrontal cortex, dorsolateral prefrontal cortex, and caudate nucleus [18]. Recent metaanalysis of neuroimaging studies in OCD confirm hypermetabolism in orbitofrontal cortex and nucleus caudatus.

Repetitive transcranial magnetic stimulation (shortly rTMS) provides a relatively noninvasive probe of cortical function. In rTMS, a pulsative electromagnetic field emitted from a coil placed against the scalp induces focal electrical current in the underlying cerebral cortex. Cortical activity can be stimulated or inhibited by rTMS. The effect is neuronal depolarization within the depth of 2cm from head surface [5]. Mechanism of action of TMS in neuropsychiatric disorders is not yet fully known. The anticonvulsant effect, modulation of monoamine neurotransmission, alterations in β receptors, reduction of 5HT₂ receptors in frontal cortex, increased density of 5HT_{1a} under the coil, effect on c-fos mRNA gene expression and increased amount of BDNF were described in animal or human subject studies. It has been already demonstrated that low frequency stimulation (1Hz) has an inhibitory effect on motor cortex that is mediated to the prefrontal cortex and high frequency excitatory effect, respectively [15].

There are few data about therapeutic application of TMS in the treatment of obsessive compulsive disorder. In a randomized trial of left and right prefrontal 20 Hz stimulation in 12 patients with OCD, Greenberg et al [7,8] found that a single session of right prefrontal rTMS-decreased compulsive urges for 8 hours. Mood was also transiently improved, but there was no effect on anxiety or obsessions. Only two other studies [1] have examined possible therapeutic effects of rTMS in OCD. A double-blind study using right prefrontal slow (1 Hz) rTMS and a less-focal coil failed to find statistically significant effects greater than sham. In contrast, another open study [17] in a group of 12 OCD patients, refractory to standard antidepressant treatments, who were randomly assigned to right or left prefrontal fast rTMS, found that clinically significant and sustained improvement was observed in a third of patients. We observed benefit in one patient with resistant OCD after 15 days of 1 Hz left rTMS [13]. There is impossible to rule out the possibility of placebo effect in these studies because of absence of a sham treatment. One case study showed clinical improvement after 10 days of 1 Hz left rTMS but not effect after 10 days sham rTMS [16].

The general aim of our study was to evaluate the therapeutic effect of the low frequency rTMS in serotonin reuptake inhibitor (SRI) resistant OCD patients. Zero hypothesis was:

- rTMS will have no impact on the symptomatology in the patients with OCD

Alternative hypothesis was:

- rTMS will have significant impact on the symptomatology of OCD comparing with placebo application (sham).

Metod

Subjects:

Patients treated in Psychiatric Centre Prague with OCD, non-responders to SRIs (after 8 weeks of treatment) were screened to the study. Thirty three patients were randomly allocated to active rTMS or sham rTMS after initial assessment.

Including criteria:

- a) ICD-10 research criteria for OCD and OCD diagnosed according to DSM IV, confirmed using the Mini-International Neuropsychiatric Interview – M.I.N.I [19, 14]
- b) Non-responders to 8-weeks SRIs therapy
- c) Age 18–45 years
- d) Written informal consensus

Excluding criteria:

- a) Major depressive disorder according to ICD-10
- b) Risk of suicidality
- c) 17-item HAMD more than 16
- d) Organic psychiatric disorder
- e) Psychotic disorder in history
- f) Abusus of alcohol or other drugs
- g) Serious somatic disease
- h) Patients using non-prescribed medication
- i) Gravidity or lactation
- j) Epilepsy or pathological EEG
- k) Patients with implantants or pacemaker

Including criteria were confirmed with two independent raters.

Criteria for exclusion during the study (drop out):

- a) Fulfilling the excluding criteria
- b) Non-compliance
- c) Decision of researcher in the case of somatic problems of patients
- d) More than 25% increase of anxiety symptoms according to HAMA

The study was designed as a double-blind, therefore rTMS was performed by a psychiatrist trained in rTMS application and rating was provided by another trained psychiatrist blind to rTMS therapy. Patients were randomly assigned to the active and sham groups using block design methods.

Technical devices

Magstim Super Rapid stimulator (Whitland, UK) with an air cooled, figure-eight 70-mm coil was used for 10 sessions (5 sessions per week for 2 weeks) The frequency of 1 Hz rTMS at 110% of motor threshold (MT) was administered over the left dorso-lateral

Table 1: Time table for using the measures

measurements	Week 0	Week 2	Week 4
ICD-10	X		
MINI	X		
CGI-S	X	X	X
Y-BOCS	X	X	X
HAMA	X	X	X
BAI	X	X	X
PET scan	X	X	

Legend: **ICD-10** = The International Classification of Disorders, 10. revision; **MINI** = Mini-International Neuropsychiatric Interview; **CGI-S** = Clinical Global Impression-Severity; **CGI-I** = Clinical Global Impression - Improvement; **Y-BOCS** = Yale-Brown Obsessive Compulsive Scale; **PDSS** = Panic Disorder Severity Scale; **HAMA** = Hamilton Anxiety Rating Scale; **BAI** = Beck Anxiety Inventory

Table 2: Patients included and excluded from the study

Patients referred to the PCP	39
Including criteria reached	33
Male: female	21:12
Drop outs	3
Completers	30

Table 3. Demographic data

	OCD		statistics
	rTMS	Sham	
Number	18	12	
Age	28.9 ± 7.7	33.4 ± 8.7	UTT: n.s.
Gender; Male: Female	13 : 5	5 : 7	FET: n.s.
Education; basic : secondary : university	5 : 13 : 0	1 : 9 : 2	chi2: n.s.
single : married	16 : 2	9 : 3	FET: n.s.
antidepressant medication (equivalent of paroxetine)	70.0 ± 27.8 mg	65.0 ± 36.1 Mg	UTT: n.s.
frequency of adjuvant antipsychotic medication	13: 5	4:8	FET: n.s.
duration of disorder	14.6 ± 7.3	16.3 ± 7.9	UTT: n.s.

UTT – unpaired t-test; FET - Fisher's exact test, chi2 – Chi-square test with Yates' correction

prefrontal cortex (DLPFC) for 30 min., with the total number of 1800 pulses per session. The left DLPFC stimulation site was defined as the region 5 cm rostral in the same sagittal plane as the optimal site for MT production in the right abductor pollicis brevis. MT was assessed as the lowest strength of TMS needed to elicit 5 or more electromyographic responses (EMG, Neurosign 400 equipment) $\geq 50 \mu\text{V}$ within ten trials. The sham stimulation was defined with a coil diverted by 90 degrees over the same area and same intensity and design as real rTMS.

Ratings

Subjects were rated before the treatment (week 0), after 14 days (10 days of stimulation) (week 2) and 2 weeks after stimulation (week 4). General psychopathology was assessed by Clinical Global Impression (CGI) [10]; anxiety was objectively measured with HAMA – Hamilton Rating Scale for Anxiety [11] and self report BAI – Beck Anxiety Inventory [2]. Severity of obsessive compulsive disorder was measured with Y-BOCS – Yale-Brown Obsessive Compulsive Scale [6]. Rating scales were administered the day before first rTMS administration, then after 2 weeks (after 10 stimulation) and after 4 weeks (2 weeks after last stimulation).

Ethical issues

Investigation was carried out in accordance with the latest version of Helsinki declaration. Written informed consent was obtained from all subjects after the nature of the procedures had been fully explained. The local ethic Committee of Prague Psychiatric Center and Mental Hospital Bohnice approved this project.

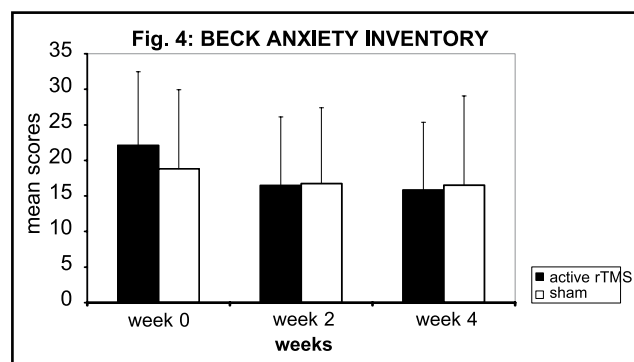
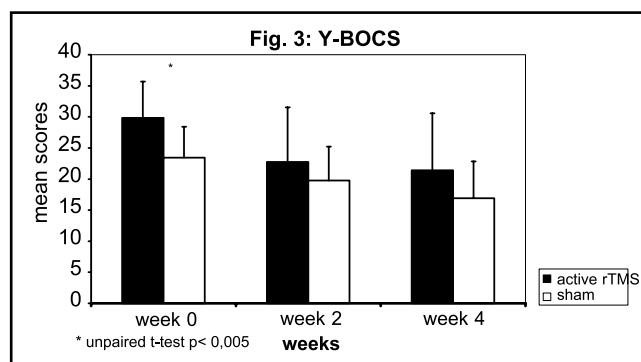
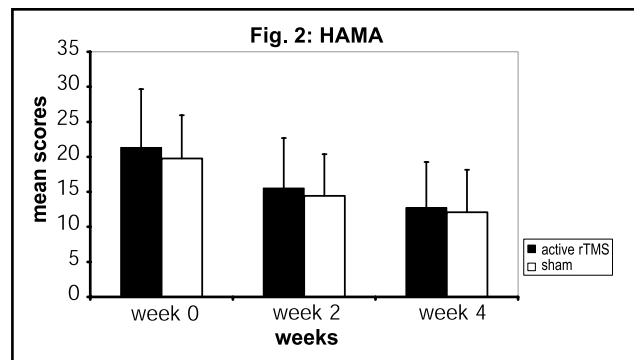
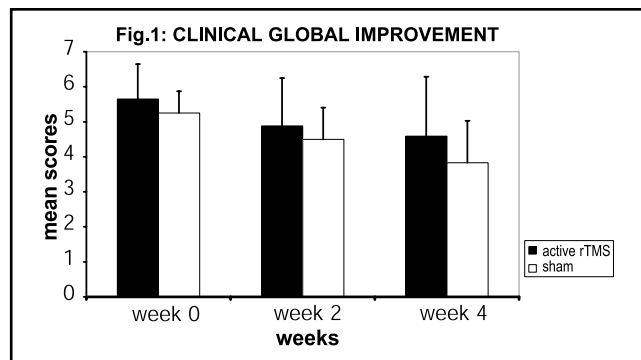
Statistics

All data are presented as the mean and SD. Patient's demographic and baseline clinical characteristics were compared between treatment groups and analyzed using the two-sample t-test or the Mann-Whitney U test and chi-square test or Fisher's exact test for continuous and categorical variables, respectively. Results were analyzed using non-parametric repeated measure analysis of variance (Friedman's test with post hoc Wilcoxon signed rank test with a Bonferroni correction for multiple comparisons) and Mann-Whitney U-tests for intra- and inter-group comparisons respectively. In case of a significant difference between groups before treatment a rank transformation-analysis of covariance (ANCOVA) with baseline score as a covariate was performed [3]. Results were considered significant if $p < 0.05$. Statistics were performed by Statsoft Statistica version 7.0 software.

Table 4: The rating scales before the treatment

	rTMS		Sham		Statistics test: p-value
	mean	SD	mean	SD	
CGI – S	5,647	0,9963	5,25	0,6216	MW: n.s.
HAMA	21,35	8,299	19,75	6,21	MW: n.s.
Y-BOCS	29,82	5,876	23,42	4,999	UTT: p < 0,005
BAI	22,12	10,36	18,83	11,09	MW: n.s.

UTT – unpaired t-test; MW = Mann-Whitney U test



Results

Description of the patient group

There were 39 patient referred to the Prague Psychiatric Centre for pharmacoresistent obsessive-compulsive disorder. Thirty-three of them fulfilled the including criteria to the study and were randomized to two study groups. The patient had been receiving stable pharmacological treatment (antidepressants and some of them low doses of antipsychotics) for 8 weeks before study enrollment. There were three patients drop out at the beginning, when they refused the stimulation procedure because of strong obsessive thoughts induced before rTMS (Table 2).

There were no statistically significant differences between the active and sham groups in terms of demographic characteristics such as age, education, marital status, duration of the disorder and dose of antidepressant medication (calculated to the paroxetine equivalents: paroxetine 20 mg = citalopram 20 mg or fluoxetine 20 mg, or sertraline 50 mg or venlafaxin 75mg). The demo-

graphic and medication baseline data of thirty completers are presented in the Table 3.

There were no statistically significant differences between the active and sham groups in the average scores of psychopathology rating scales of CGI, HAMA and BAI, but there was significant difference in rating scale Y-BOCS; the rTMS group had statistically significantly higher scores than sham group (unpaired t test: p<0,005). The baseline data from rating scales are presented in the Table 4.

Pharmacotherapy

All patients followed with medication (SRIs eventually in combination with stable doses of antipsychotics) which they used before without any change during the study. The average doses of antidepressant medication and frequency of adjuvant therapy with antipsychotics are given on Table 3. The mean doses (unpaired t-test) and frequencies (Fischer exact test: n.s) of the psychopharmacops do not differ between groups.

Table 5: Mean scores in rating scales during the treatment

	rTMS		sham		Statistics test: p-value	
	mean	SD	mean	SD		
CGI – S	Week 0	5.647	0.9963	5.25	0.6216	n.s.
	Week 2	4.882	1.364	4.5	0.9045	n.s.
	Week 4	4.588	1.698	3.833	1.193	n.s.
HAMA	Week 0	21.35	8.299	19.75	6.21	n.s.
	Week 2	15.53	7.16	14.42	5.946	n.s.
	Week 4	12.76	6.505	12.08	6.067	n.s.
Y-BOCS	Week 0	29.82	5.876	23.42	4.999	UTT p < 0.005
	Week 2	22.76	8.757	19.75	5.446	n.s.*
	Week 4	21.41	9.159	16.92	5.915	n.s.*
BAI	Week 0	22.12	10.36	18.83	11.09	n.s.
	Week 2	16.47	9.631	16.75	10.64	n.s.
	Week 4	15.82	9.528	16.5	12.57	n.s.

* An analysis of covariance (ANCOVA) with baseline score as a covariate

Rating scales

CGI – severity

There were not significant differences in the severity scores of Clinical Global Impression (CGI) in both groups in the beginning (see Table 5). Severity scores dropped significantly in both groups during the treatment, but the differences between the groups after two weeks of treatment and after another two weeks are not significant (Mann Whitney U test: n.s.).

HAMA

In the objective rating scale intended for measuring overall symptoms of anxiety (not solely focused on obsessive compulsive symptoms), statistically significant decrease of total scores occurred in both groups. However, no significant difference in decreases of total scores was found between two treatment groups (Mann Whitney U test: n.s – see Table 5).

Y-BOCS

Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is an instrument for specific assessment of an obsessive compulsive disorder. It is the most sensitive instrument for this disorder. Unfortunately, there was significant difference in the mean total score of Y-BOCS between active and sham groups in the beginning (unpaired t-test, $p < 0,005$). In both groups of patients there was a significant decrease in total scores during study period. The difference between the groups is not statistically significant in week 2 and week 4 (an analysis of covariance (ANCOVA) with baseline score as a covariate: n.s.)

BAI

There were no significant differences in the severity scores of Beck Anxiety Inventory (BAI) – general subjective scale for anxiety symptoms – in both groups in the beginning. Time path of BAI scores is similar to those

of HAMA. Statistically significant decreases of total BAI scores occurred in both groups. However, there was not significant difference between rTMS treatment of sham placebo treatment (Mann Whitney U test: n.s – see Table 5)

Tolerability and safety

There were no seizures, headaches, neurological and cognitive difficulties occurred after rTMS.

Discussion

Referring back to our hypotheses, our study has confirmed the zero hypotheses – low frequency rTMS of left prefrontal cortex had no impact on the symptomatology in the patients suffering with SRIs resistant obsessive compulsive disorder. It corresponds with results of Sachdev et al [17] rTMS study (10 Hz, 110% MP for 2 weeks randomly used to either right or left prefrontal cortex), with only one quarter response rate of patients with resistant OCD. The efficacy of rTMS of the right prefrontal cortex (we used left side) for patients with OCD was also studied under double-blind, placebo-controlled conditions [1]. Patients were randomly assigned to 18 sessions to real (N=10) or sham (N=8) rTMS (treatment lasted 20 minutes, frequency 1Hz, intensity 110% for real and 20% for sham condition). No significant changes were detected in either group after treatment. Authors conclude with the same result, that low-frequency rTMS failed to produce significant improvement of OCD symptomatology.

On the other hand, in this study we treated chronic patients suffering with OCD, who were resistant to previous antidepressant medication. There was relatively long mean previous duration (about 15 years) of the disorder in this population. The question is how can rTMS work in less chronic patients? Another question

is, if the place of stimulation and low frequency of stimulation are optimal for OCD patients?

Some studies showed that for rTMS efficacy are very important good parameters of intensity, number of pulses or number of sessions [4]. We use adequate intensity and number of pulses per session, but 10 sessions could be insufficient. Some rTMS studies in patients with depression showed that 10 sessions could be insufficient even in therapy in patients with depression [4]. The response is faster in patients with depression during SRI therapy than in patients with OCD. Twenty sessions of rTMS have similar efficacy as electroconvulsive therapy in patients with depression [9]. Maybe for rTMS effect in patients with OCD is necessary rTMS therapy more longer than 10 or 20 sessions.

Another question is, if the place of stimulation and low frequency of stimulation are optimal for OCD patients? Choice of the place and low frequency was done according results of hypermetabolism on PET in this region and hypothesis that low frequency rTMS reduce hyperexcitability and hypermetabolism [12].

There are several another limitations of our study that to be mentioned. The patients treated with active rTMS presented at the beginning statistically significantly more severe obsessive compulsive symptoms in Y-BOCS, the most important of the scales. Although no significant differences between treatment groups were detected, the patients treated with real rTMS had a somewhat greater reduction in Y-BOCS. Our negative findings may be related to type II error. There is also a small group size. Therefore the comparison of these two groups have limitations.

Conclusion

Low frequency rTMS administered over the left dorso-lateral prefrontal cortex during 10 sessions did not differ from sham rTMS in facilitating the effect of antidepressants in OCD patients in our study. Further studies are indicated to assess the efficacy of rTMS in OCD and to clarify the optimal stimulation characteristics.

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