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Repetitive Transcranial Magnetic Stimulation (rTMS) improves symptoms and reduces clinical illness in patients suffering from OCD – Results from a single-blind, randomized clinical trial with sham cross-over condition

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ABSTRACT

Objectives: Both psychotherapeutic and psychopharmacological methods are used in the treatment of patients suffering from obsessive-compulsive disorders (OCD), and both with encouraging but also mixed results. Here, we tested the hypothesis that repetitive Transcranial Magnetic Stimulation (rTMS) improves symptoms and reduces illness severity in patients suffering from treatment-resistant OCD.
Methods: A total of 21 patients (57% females; mean age: M = 35.8 years) suffering from treatment-resistant OCD were randomly assigned either to an rTMS-first-sham-second, or a sham-first-rTMS-second condition. Treatment sessions lasted for 4 weeks with five sessions per week, each of about 50 min duration. Symptoms were assessed via both self- and expert-ratings.
Results: Both self- and expert-reported symptom severity reduced in the rTMS condition as compared to the sham condition. Full- and partial responses were observed in the rTMS-condition, but not in the sham-condition.
Conclusions: The pattern of results from this single-blind, sham- and cross-over design suggests that rTMS is a successful intervention for patients suffering from treatment-resistant OCD.

1. Introduction

Worldwide, 1–3 % of the population suffers from obsessive–compulsive disorders (OCD) (Kessler et al., 2005; Ruscio et al., 2010; Karno et al., 1988). Symptoms of OCD include persistent intrusive thoughts (obsessions), repetitive and ritualistic behaviors (compulsions), and excessive anxiety (Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000). Suffering from OCD is associated with a dramatically reduced quality of life and increased risk of poor social interactions and loss of employment, and is therefore accompanied by a high risk of disability and morbidity (Hollander, 1996). Psychopharmacological and psychotherapeutic interventions are both employed in the treatment of OCD. Cognitive-behavioral therapy is as effective as psychopharmacological interventions (Franklin and Foa, 2011), though patients suffering from OCD are generally treated psychopharmacologically and specifically with selective serotonin re-uptake inhibitors (SSRIs) or clomipramine, a tri-cyclic antidepressant (cf. Wu et al., 2012). Both psychopharmacological and psychotherapeutic interventions are successful in 40–70 % of cases (Foa et al., 2005;

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Swedo and Snider, 2004), though residual symptoms without full remission are often observed (Akerman and Greenland, 2002; Mataix-Cols et al., 2002), again increasing the risk for disability and morbidity (Hollander, 1996).

New avenues in the treatment of OCD have been explored in response to these rather modest remission rates. Whereas for instance the treatment with adjuvant memantine seems promising (Hezel et al., 2009; Stewart et al., 2010; Ghaleiha et al., 2013; Haghighi et al., 2013), in recent years repetitive Transcranial Magnetic Stimulation (rTMS) has attracted increased interest. Briefly, rTMS is a noninvasive technique to activate and modify the activity of the neurons. Whereas the underlying mechanisms are not fully understood, there is broad agreement (see Ridding and Rothwell, 2007; for extensive overview) that the technique consists of depolarization or hyperpolarization in the neurons of the brain, most likely in the axon. However, in contrast to electroconvulsive interventions in which electrodes applied to the skull transmit pulses of minimum electrical power to induce depolarization and hyperpolarization in the neurons, these effects are achieved with electromagnetic fields. Ridding and Rothwell (2007) note that a stimulator produces a magnetic field of the same order as that of an MRI scanner, though the magnetic field is switched on and off at a very high rate per ms, inducing an electrical current in a specific area of the skull, which is to say in the area of the brain under the coil. In other words, rTMS uses electromagnetic induction to induce weak electrical currents using a rapidly changing magnetic field, which in turn causes an electrical current in specific or general parts of the brain with little discomfort. Moreover, the difference between Transcranial Magnetic Stimulation (TMS) and rTMS is in the repetition rate of the electromagnetic stimulations; whereas single pulses of TMS produce short responses, repeated pulses can have more prolonged effects on the brain (again, see Ridding and Rothwell (2007) for an extensive overview and explanations).

rTMS has been applied in the treatment of obsessive-compulsive disorders (OCD). The Table uploaded as supplementary material gives a brief overview of studies undertaken in recent years and is based on three reviews. The key message is that rTMS may favorably influence OCD, though the pattern of results is mixed. (Blom et al. 2011; Jaafari et al. 2012)

It is unclear, why results have been mixed, though it is possible that methodological differences in samples, rTMS-positioning, differences in rTMS-stimulation (duration, intensity, frequency), and different sham-/control-conditions might have contributed to this inconclusive pattern. The aim of the present study was therefore to gain further insight into the usefulness of rTMS in treating patients suffering from OCD. To do so, a single-blind, randomized clinical trial with sham cross-over condition was undertaken. We believe that the sham-cross-over condition has the advantage of further exploring any prolonged effect of rTMS on the brain, and, ultimately, on patients' behavior.

Following Ruffini et al. (2009), Mantovani et al. (2010), Ma et al. (2014), and Berlim et al. (2013) we expected improvements in symptoms of OCD over time as compared to a sham-condition. More specifically, we expected that symptoms would improve during the treatment, irrespective of its timing, that is, irrespective of whether treatment was administered first before the sham-condition or after the sham-condition. Correspondingly, we expected no symptom improvements under sham conditions, irrespective of whether the sham condition followed or preceded the treatment condition. In the latter case, however, we expected that the baseline level of the sham-condition, that is to say, the last measurement of the treatment condition, would be lower, as compared to the baseline of the condition in which the sham was administered first.

2. Methods and materials

2.1. Sample

The participants were 21 out-patients (12 females (57%); mean age, M = 35.86, SD = 11.02), diagnosed according the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV) criteria (American Psychiatric Association, 2000) as suffering from OCD. Patients were fully informed about the study aims and procedure, and about the confidential nature of data selection and data handling, and gave their written informed consent. The study took place in the psychiatric ward of the Research Center for Behavioral Disorders and Substances Abuse (Farshchian Hospital; Hamadan University of Medical Sciences, Hamadan, Iran). The local ethics committee approved the study, and the entire study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.[1]

2.2. Inclusion criteria

Patients were enrolled in the study if the following inclusion criteria were met: (1) diagnosis by a psychiatrist[2] of current OCD according to the DSM IV (American Psychiatric Association, 2000) on the basis of a structured psychiatric interview (SCID; First et al., 1997). (2) Yale–Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989) score of 17 points or higher (see below). (3) Within the previous 10 weeks no clinical response had been achieved following at least three separate antidepressant trials of sufficient dose (included clomipramine) and CBT. (4) Willing and able to consent to the study based on their ability to provide a spontaneous narrative description of the key elements of the study. (5) After a careful neurological interview and the inspection of medical records, no seizures or further neurological disorders or major medical issues were reported or recorded. (6) No comorbid psychiatric disorders. (7) No current alcohol and other drug use. (8) Age between 18 and 65 years (see also Table 1).

2.3. Exclusion criteria

Patients were not included in the study, if: (1) the inclusion criteria mentioned above were not met. (2) From the medical and neurological records it turned out that the patient had metal implants. (3) Female participants were pregnant or breast-feeding or intended to become pregnant during the period of the study. (4) There was a history of DSM IV substance dependence in the last 6 months. (5) Acute suicidality. (6) With respect to concomitant medications: (a) intake of more than 1 mg/d alprazolam (or equivalents), (b) monoamine oxidase inhibitors, (c) and/or bupropion due to its associated increased risk for seizures. Further, (7) patients were excluded from the study in case of severe adverse effects, and if the patient withdrew from the study.

Of 32 patients initially approached, 21 patients (65.63% of those approached) were enrolled, assessed, and randomly assigned to the study conditions. Ten patients were randomly assigned to the rTMS-first-condition; 11 patients were assigned to the sham-first-condition. During the four week duration of the study there were no drop-outs.

Descriptive and statistical comparisons of the target and control groups are reported in Table 1. At baseline, target and control

[1] The clinical trial number is: Irct ID: IRCT201308041743N11; www.irct.ir.

[2] Note that experts responsible of the diagnosis of the obsessive-compulsive disorders were not further involved in the treatment of the patients enrolled in the study.

Table 1
Descriptive and statistical overview at baseline, separated by the rTMS-first-sham-second and the sham-first-rTMS-second conditions.

	Condition		Statistics
	rTMS-first-sham-second	Sham-first-rTMS-second	
Age (years)	34.90 (5.91)	36.55 (3.95)	$t(19) = 1.18$, $p = .25$
Gender (male/female)	7/3	5/6	$X^2(df = 1, N = 21) = 1.29$, $p = .26$
Highest educational level (mandatory school/diploma/university)	2/5/3	4/2/2	$X^2(df = 2, N = 21) = 2.41$, $p = .30$
Civil status (single/married)	5/5	6/5	$X^2(df = 1, N = 21) = .43$, $p = .83$
Type of OCD (contamination/symmetry-ordering/counting/pure obsessions)	5/3/1/1	5/2/2/2	$X^2(df = 3, N = 21) = .82$, $p = .84$

groups did not differ with respect to age, gender, education, civil status, and type of OCD).

2.4. Study design and randomization

The present study was a four-week, randomized, single-blind, sham, controlled clinical trial with cross-over design. Patients suffering from OCD were recruited between fall 2013 and spring 2014 in the Farshchian Hospital of Hamadan (Iran). In addition to standardized SSRI- or clomipramine medication at therapeutic dosages and CBT, all patients were treated with rTMS for two weeks and with an rTMS sham condition for two weeks. Those starting with the rTMS intervention for two weeks, received the sham interventions afterwards for two weeks; those patients first undergoing the sham condition for two weeks, were then treated with rTMS intervention for a further two weeks. To randomize patients either to the intervention first or the sham first condition, 10 blue (rTMS condition) and 11 red chips (sham condition) were put in an opaque and closed ballot box and stirred. A psychologist not involved in the study drew a chip, and patients were assigned either to the rTMS-first or to the sham-fist condition according to the chip color drawn, though patients were not aware to which condition they had been assigned. One week before its start and throughout the study patients were treated with a standard SSRI or clomipramine at therapeutic dosages for at least 10 consecutive weeks.

2.5. Tools

2.5.1. Assessing OCD with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; self-rating)

The Y-BOCS (Goodman et al., 1989) is a self-rating instrument to assess obsessive-compulsive disorders and consists of ten items and answers are given on 5-point Likert scales ranging from 0 (lowest severity) to 4 (highest severity), with higher sum scores reflecting more severe OCD (Cronbach's alpha = .89).

Patients completed the Y-BOCS three times; at the beginning of the study (baseline), after two, and after four weeks.

2.5.2. Assessing changes in illness severity and improvement (experts' ratings)

Experts assessed the illness severity with the clinical global impression scale (CGI; Guy, 1976). This consists of one item asking how mentally ill a patient is currently. Answers are given on a 7-point Likert rating scale ranging from 1 (normal; not at all ill) to 7 (among the most extremely ill patients), a higher score therefore reflecting greater illness severity. Illness severity was assessed three times; at baseline, after two and after four weeks.

Treatment improvement was likewise assessed with the CGI. The item asks about global improvement, and answers are given on a 7-point Likert rating scale ranging from 1 (very much improved) to 7 (very much worse), a higher score thus reflecting greater deterioration in condition. Illness improvement was assessed two times; after two and after four weeks, but not at baseline. Psychiatrists and psychologists responsible for this rating were not further involved in the treatment.

2.6. Interventions; intervention and sham conditions

We used the 70 mm Double Air Film Coil, Magstim (The Magstim Company Ltd, Spring Gardens, Withland, Carmartenshire, UK). The intervention involved bilateral repetitive transcranial magnetic stimulation (rTMS) applied to the dorsolateral prefrontal cortex according to the following protocol: high frequency stimulation was applied at 20 Hz, in 750 total pulse, in 25 trains with 1.5 s duration to the left dorsolateral prefrontal cortex (DLPFC) at 100% of the rest motor threshold (RMT), which was followed with same parameters at right prefrontal cortex, that is to say: The intensity for each pulse of stimulation was exactly equal of RMT (neither above nor below RMT). RMT was determined by finding the threshold of visible movements of the right thumb (abductor pollicis brevis) by the traditional International Federation of Clinical Neurophysiology (IFCN) method. There was no gap between the device and the skull. Total stimulation duration was approximately 25 min per cortex site, totaling 50 min for every intervention session. A cortex site was targeted by the "5-cm method". With this method, the left DLPFC is localized 5 cm anterior from motor area along a parasagital line. At the time RMT was estimated, (by visible movements of abductor pollicis brevis muscle), the place of motor area was defined. The right DLPFC is in symmetric place of the left hemisphere. Intervention was performed for five sessions per week.

For the sham condition, stimulation was made at the site of active treatment but with only the side edge resting on the scalp. 'Stimulation' was administered as high frequency left and high frequency right 'stimulation' for 50 min; again, there was no gap between the device and the skull, though the coil was angled 45–90° away from the skull in a single-wing tilt position. This method produces sound and some somatic sensation (e.g., contraction of scalp muscles) similar to those during active stimulation, but with minimal direct brain effects. Additionally, participants could not see the position of the stimulating coil; accordingly, patients remained blind to the treatment condition. As with the genuine intervention, the sham was performed for five sessions per week. Psychiatrists responsible for the treatment were not responsible for the assessment of patients' illness severity and improvement.

2.7. Statistical analysis

Demographic and symptom characteristics were compared at baseline between the target and control group with X^2-tests and with single t-tests. A series of ANOVAs for repeated measures was performed with the factors Time (3 time points for Y-BOCS scores; 3

time points for CGI severity scores, and 2 time points for CGI improvement scores) and Group (rTMS-first vs. Sham-first), and with Y-BOCS scores, CGI severity scores, and CGI improvement scores as dependent variables. Where appropriate, post-hoc tests with the Bonferroni–Holm correction for p-values were used, applying single t-tests. To compensate for any deviations from sphericity, statistical tests were performed using Greenhouse–Geisser corrected degrees of freedom, though throughout the paper the original degrees of freedom are reported with the relevant Greenhouse–Geisser epsilon value (ε). For ANOVAs, effect sizes were indicated with the partial eta squared (η^2), with $.059 \geq \eta^2 \geq .01$ indicating small [S], $.139 \geq \eta^2 \geq .06$ indicating medium [M], and $\eta^2 \geq .14$ indicating large [L] effect sizes.

Next, Y-BOCS values were also aggregated as a function of condition, rTMS- or sham-intervention. That is to say, irrespective of the study design, all Y-BOCS values before and after the rTMS-intervention were aggregated, and all Y-BOCS values before and after the sham-condition were aggregated, leading to a new dummy-sample of $n = 42$. Then, two statistical calculations were performed. First, an ANOVA for repeated measures was performed with the factors Intervention (rTMS vs. sham), Time (pre vs. post) and the Intervention by Time interaction, and with the Y-BOCS values as the dependent variable. Second, a X^2-test was performed to calculate the association between treatment condition (rTMS vs. sham) and treatment response (see below).

Based on Pallanti and Quercioli (2006), the following categorizations of treatment response were made, based on the percentage reduction of the Y-BOCS score. Pallanti and Quercioli (2006) proposed a threshold of 35% or more in Y-BOCS reduction for "full response." 25–35 % for "partial response," and less than 25% for "no response."

The level of significance was set at $p \leq .05$, and all statistics were processed using SPSS® 20.0 (IBM Corporation, Armonk NY, USA) for Apple McIntosh®.

3. Results

3.1. Obsessive-compulsive behavior (self-rating: Y-BOCS values) and Clinical Global impression values (severity and improvement; experts' ratings) over time and between the rTMS and sham condition.

Table 2 reports all descriptive and inferential statistics.

Y-BOCS values decreased significantly over time. No group differences were observed. The significant Time by Group Interaction showed that Y-BOCS values decreased over time in the rTMS condition, but not in the sham-condition. Post-hoc analyses with Bonferroni-Holm corrections for p-values showed that in the rTMS-first-sham-second-condition the first Y-BOCS values (baseline) were significantly higher than at the second (week 2) or third (week 4) time points; no significant mean differences were found between the second (week 2) and third (week 4) time points. By contrast, in the sham-first-rTMS-second-condition the first Y-BOCS values (baseline) did not differ from the second (week 2) condition. The third (week 4) Y-BOCS values were significantly lower than both the first (baseline) and second (week 2) time point values (see Fig. 1).

3.2. Obsessive-compulsive symptoms: response rates of Y-BOCS values (self-rating)

Table 3 reports the response rates (descriptive and X^2-statistics), separately by the rTMS-first-sham-second and the sham-first-rTMS-second conditions. Between baseline and second week, full and partial response was observed in the rTMS-first-sham-second condition, but not in the sham-first-rTMS-second condition. By contrast, from the second to the fourth week, full and partial response was observed in the sham-first-rTMS-second condition, but not in the rTMS-first-sham-second condition.

3.3. Clinical global impression values: severity

CGI severity values decreased significantly over time (Table 2). The rTMS-first-sham-second group had more favorable scores than the sham-first-rTMS-second condition. The significant Time by Group Interaction showed that CGI severity values decreased over time under the rTMS condition, but not under the sham-condition. Post-hoc analyses with Bonferroni-Holm corrections for p-values showed that in the rTMS-first-sham-second-condition the first CGI severity values (baseline) were significantly higher than the second (week 2) or third (week 4) time point values; no significant mean differences were found between the second (week 2) and third (week 4) time points. By contrast, in the sham-first-rTMS-second-condition the first CGI severity values (Baseline) did not differ from those in the second (week 2) condition. The third (week 4) Y-BOCS values were significantly lower than both the first (baseline) and second (week 2) time point values.

3.4. Clinical global impression values: improvements

Irrespective of the sequence, greater improvements were observed in the rTMS-condition than in the sham condition (Table 2).

3.5. Aggregation of the Y-BOCS scores as a function of intervention (rTMS vs. sham)

Y-BOCS values were also aggregated as a function condition, namely rTMS versus sham-intervention. That is to say, irrespective of the study design, all Y-BOCS values before and after the rTMS-intervention were aggregated, and all Y-BOCs values before and after the sham-condition were aggregated, leading to a new dummy-sample of $n = 42$. Then, two statistical calculations were performed. First, an ANOVA for repeated measures was performed with the factors Intervention (rTMS vs. sham), Time (pre vs. post) and the Intervention by Time interaction, and with the Y-BOCS values as the dependent variable. Second, a X^2-test was performed to calculate the association between treatment condition (rTMS vs. sham) and treatment response (see below).

All descriptive and statistical results are reported in Table 4a and 4b.

Y-BOCS values decreased significantly from the first to the second assessment. Y-BOCS values did not differ between the two treatment conditions (rTMS vs. sham). The significant Time by Group − interaction showed that Y-BOCS values decreased over time in the rTMS-condition but not in the sham condition (Table 4a; see also Fig. 2).

Full or partial responses were observed only in the rTMS- condition, and not in the sham condition (Table 4b).

4. Discussion

The key findings of the present study are that repetitive Transcranial Magnetic Stimulation (rTMS) led to improvement in the symptoms and clinical global impression of patients suffering from OCD, as compared to a sham condition. Moreover, changes in symptoms were apparent in both the self-ratings and expert ratings, thus enhancing the validity of the pattern of results. Further, and most important, once the rTMS treatment had been completed, OCD symptoms (self- and experts' ratings) remained low,

Table 2
Descriptive and statistical overview of the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) scores, and the Clinical Global Impression scores (severity; 3 time points; improvements: 2 time points), and separated by the rTMS-first-sham-second and the sham-first-rTMS-second conditions.

Statistics											
	Y-BOCS			Group		Time		Group × time		Greenhouse-Geisser epsilon	Post-hoc analyses
	Baseline	After 2 weeks	After 4 weeks								
	M (SD)	M (SD)	M (SD)	F	eta^2	F	eta^2	F	eta^2	ε	
rTMS-first-sham second	30.40 (6.54)	19.10 (7.74)	20.10 (6.62)	1.79	.086 [M]	48.45***	.72 [L]	19.45***	.51 [L]	.864	BL > w2 and w4 W2 = w4
Sham-first-rTMS second	30.09 (8.08)	29.91 (7.80)	22.00 (7.89)								BL = w2 BL and w2 > w4
	CGI severity										
	Baseline	After 2 weeks	After 4 weeks	Group		Time		Group × Time		Greenhouse-Geisser epsilon	Post-hoc analyses
	M (SD)	M (SD)	M (SD)								
rTMS-first-sham second	5.00 (.94)	2.60 (1.51)	2.60 (1.35)	5.59*	.227 [L]	72.62***	.792 [L]	26.49***	.582 [L]	.943	BL > w2 and w4; ps < .01 W2 = w4
Sham-first-rTMS second	5.09 (1.22)	5.09 (1.04)	3.45 (1.04)								BL = w2 BL and w2 > w4; ps < .01
	CGI improvements										
	Baseline	After 2 weeks	After 4 weeks	Group		Time		Group × Time		Greenhouse-Geisser epsilon	–
	M (SD)	M (SD)	M (SD)								
rTMS-first-sham second	–	6.30 (.82)	3.70 (.82)	.37	.019 [S]	1.02	.051 [S]	86.53*** [L]	.82	1.00	
Sham-first-rTMS second	–	4.09 (.70)	6.18 (.75)								

Notes: CGI = Clinical Global impression; symptom severity: lower scores indicate a lower symptom severity. Degrees of freedom: Group: (F(1, 19), Time and Time by Group interaction: F(2, 38). * = p < .05; *** = p < .001. [S] = small effect size; [M] = medium effect size; [L] = large effect size.

Fig. 1. Y-BOCS values decreased significantly as a function of rTMS, compared to the sham-condition. Note that rTMS was applied in the rTMS-first condition from baseline to Week 2; in the sham-first condition, rTMS was applied from Week 2 to Week 4.

suggesting therefore that this treatment can have lasting effects on brain activity, and, ultimately, enduring effects on behavior.

Based on previous studies (Ruffini et al., 2009; Mantovani et al., 2010; Ma et al., 2014; Berlim et al., 2013), our hypothesis was that rTMS, as compared to the sham condition, would improve symptoms of OCD and this hypothesis was fully supported. Therefore, the present results are consistent with some previous research (Ruffini et al., 2009; Mantovani et al., 2010; Ma et al., 2014; Berlim et al., 2013), but not with all studies (Sachdev et al., 2007; Kang et al., 2009; Sarkhel et al., 2010). We believe the present results add to previous research in demonstrating favorable changes in OCD symptoms in a single-blind, randomized clinical trial with sham-condition. This hold particularly true, if we consider that the improvement in symptoms produced by the treatment persisted under the sham condition, (see Fig. 1), and if we consider that full or partial responses were observed only in the treatment-, but not in the sham condition, and within a time frame of two weeks.

The present study does not provide any direct answers as to how or why rTMS leads to the neurophysiological changes responsible for the changes in behavior. In their absence, we offer the following speculative suggestions (see Ridding and Rothwell (2007) for extensive review and discussion). First, it is thought that OCD is triggered and maintained by dysfunctional neuronal circuits in the dorsolateral prefrontal cortex (DLPFC; Leon et al., 2014; Nakao et al., 2014; Piras et al., 2013; Baxter et al., 2000; Saxena et al., 2001). In the present study, rTMS was applied to both sites of the dorsolateral prefrontal cortex. Specifically, Baxter et al. (2000) and Saxena et al. (2001) proposed that in patients suffering from OCD, DLPFC activity seemed too low to inhibit striatal and thalamic neuronal activity responsible for triggering and maintaining highly automatized behavior related to territorial and social behavior such as aggression, hygiene, and sexuality, as observed in patient with OCD.

Table 3
Descriptive and inferential statistics of response rates of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), separately by the rTMS-first-sham-second and the sham-first-rTMS-second conditions.

	From BL to week 2			From week 2 to week 4		
	Response			Response		
	Full	Partial	no	Full	Partial	no
rTMS-fist-sham-second	6	0	4	0	0	10
Sham-first-rTMS second	0	0	11	6	2	3

$X^2(df = 1, N = 21) = 9.24$, p = .002
$X^2(df = 2, N = 21) = 11.75$, p = .003

Table 4a
Descriptive and statistical overview of aggregated Y-BOCS variables as a function of treatment condition (rTMS vs. sham) and time (pre vs post-assessment.

	Time		Statistics					
	Pre	Post	Group		Time		Group × time interaction	
	M (SD)	M (SD)	F	eta^2	F	eta^2	F	eta^2
rTMS (N = 21)	30.14 (7.05)	20.62 (7.77)	.02	.000 [S]	47.43***	.543 [L]	55.66***	.582 [L]
Sham (N = 21)	24.86 (9.55)	25.24 (8.68)						

Notes: Degrees of freedom: F(1, 40). *** = p < .001. [S] = small effect size; [L] = large effect size.

Table 4b
Response rates (full response, partial response, no response) and treatment condition (rTMS vs. sham) of the aggregated Y-BOCS values.

	Response		
	Full response	Partial response	No response
rTMS (N = 21)	9	2	10
Sham (N = 21)	0	0	21

X^2(df = 2, N = 42) = 14.30, p < .001.

Therefore, to increase neuronal activity of DLPFC via rTMS to inhibit striatal activity and hence inhibit highly automatized behavior seems reasonable. Second, a possible explanation for the enduring effects of rTMS is that rTMS leads to changes in the effectiveness of synapses between the activated neurons of the DLPFC. These changes may be inhibitory (-short-term depression: STD), or excitatory (long-term potentiation: LTP), though, given the high frequency applied, we believe the effect of the intervention was more likely to be excitatory, following Ridding and Rothwell (2007) to explain the favorable effects of (r)TMS on neuronal activity. Third, changes in neuronal activity should impact on neuronal metabolism, and imaging studies have shown that rTMS does result in a significant decrease in metabolic activity as compared to control conditions (at least in patients suffering from focal arm dystonia (Siebner et al., 2003). Ultimately, these changes in neuronal circuits were mirrored in both patients' and experts' perceptions, in that symptoms of OCD decreased.

Despite the intriguing findings, various limitations warn against overgeneralization of the present data. First, the sample size was rather small, though we basically relied on effect size calculations, which are robust against sample sizes. Second, only patients willing and able took part in the study and therefore it is possible that expectations, motivations or attitudes might have biased the results. However, we note that this objection holds true for virtually every study in the field and that, importantly, the sham condition did not lead to any improvements; in other words, there was no placebo effect. Third, the pattern of results might have emerged due to further latent, but unassessed psychological and physiological factors, biasing two or more dimensions in the same direction. In this regard, we emphasize that the activation of the (DL)PFC might have favorably influenced further cognitive–emotional processes such as increased emotion regulation (cf. Yoo et al., 2007), which might have led to an increase in behavior irrespective of and unspecific to OCD. Further, Rauch et al. (1998) emphasized that symptoms of OCD do vary, and that these variations are also mirrored in different neuronal circuits: OCD with prevalently obsessive aggressive thoughts are related to an increased activity in the striatum; OCD with prevalently obsessive ordering and repetitive behavior is related to a down-activation of the striatum, and OCD with prevalently behavior of hygiene and fear of contamination was related to an increased activation in the anterior cingulate cortex (ACC). Future studies might take in consideration the broad variability of OCD symptoms and their underlying neuronal circuits, involving circuits connecting (DL)PFC, orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), striatum, basal ganglia, and thalamus, which are central to OCD pathophysiology and treatment response. Next, cognitive performance was not assessed, and there was no longer term follow-up. Future studies might investigate to what extent rTMS alters cognitive performance, sleep, and OCD symptoms in the long-term. Further, reliability of symptom severity and improvement might be increased in applying further expert and self-rating assessment tool, instead of relying exclusively on the Y-BOCS and CGI (see Gabrill et al., 2008 for extensive presentation and discussion of further experts and self-rating instruments).

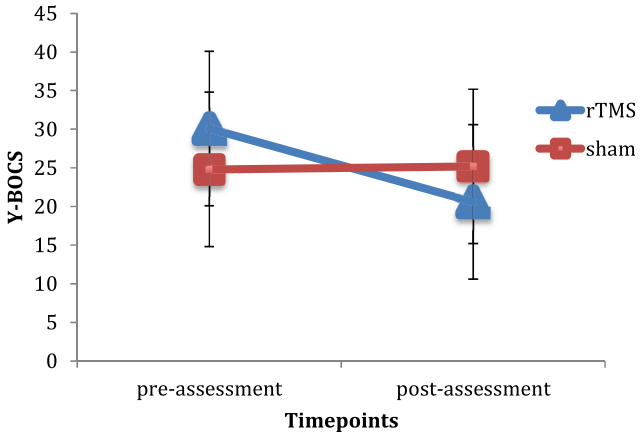

Fig. 2. Y-BOCS values decreased significantly over time in the rTMS condition, but not in the sham condition.

5. Conclusions

Compared to a sham condition, rTMS improved OCD symptoms, as assessed by both self- and expert ratings, within a time interval of two weeks. Additionally, symptoms of OCD remained low under the sham-condition following the decrease produced by the rTMS-condition.

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None to declare.

Contributions

MH, MS, LJ, MA, HB, and AR conducted the study; MH, MS, LJ, MA, EHT, and SB designed the study and wrote the study protocol. MH, MS, LJ, MA, HB, and AR gathered the data. SB performed the statistics and wrote the draft of the manuscript. All authors commented on the first draft. SB finalized the manuscript.

Conflicts of interest

All authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2015.06.020.

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