Efficacy and clinical predictors of response to rTMS treatment in obsessive-compulsive disorder (OCD): A retrospective study

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Abstract

Background: Application of the repetitive transcranial magnetic stimulation (rTMS) for treating obsessive-compulsive disorder (OCD) has been promising but effects differ between patients. Knowledge about clinical predictors of rTMS response would help to increase clinical efficacy but is not available so far.

Methods: In a retrospective study, we investigated the efficacy of rTMS over the dorsolateral prefrontal cortex (DLPFC) or supplementary motor area (SMA) in 65 OCD outpatients recruited for the rTMS treatment from July 2015 to May 2017. Patients were divided into two groups and received either SMA rTMS or bilateral DLPFC rTMS. OCD symptoms and depression/anxiety states were measured before and after the 20th session of rTMS. Additionally, we performed a binary logistic regression analysis on the demographic variables and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) items to investigate demographic and clinical predictors for rTMS response in responders and non-responders.

Results: Patients' scores in Y-BOCS and Beck anxiety/depression inventories were significantly decreased following rTMS treatment. Specifically, 46.2% of all patients responded to rTMS, based on at least 30% reduction of the Y-BOCS scores. Stimulation target (DLPFC vs. SMA) did not significantly differ in rTMS efficacy. No significant demographic predictors were found. Interference due to obsessions and resistance against compulsions were the only two clinical predictors of rTMS treatment response that could significantly predict response failure to rTMS.

Conclusions: rTMS treatment should be adapted to the clinical profile of OCD patients including the symptoms. Patients with less intrusive and interfering thoughts might benefit more from rTMS treatment. Identifying clinical and non-clinical predictors of response are needed to personalize and adapt rTMS protocols in pharmaco-resistant OCD patients.

Background

With a lifetime prevalence of 1-3% [1], obsessive-compulsive disorder (OCD) is a frequent and disabling psychiatric disorder. It is characterized by intrusive, anxiety-provoking, interfering thoughts (obsessions), and associated repetitive behaviors (compulsions) [2]. OCD, which is frequently undertreated [3], is remarkably heterogeneous in etiology, symptoms, subtype and treatment response [4, 5]. The inclusion of OCD and related disorders in a separate category in DSM 5 is indicative that OCD cannot be simply viewed as a unitary disorder with distinct symptoms. Due to such heterogeneity, approximately 40–60% of OCD patients remain treatment-refractory to current first-line therapies [6-8]. Accordingly, researchers and clinicians try to develop novel therapeutic strategies through a better understanding of OCD pathophysiology [3, 9].

Previous studies in humans and animal models suggest that functional abnormalities of the cortico-striato-thalamo-cortical (CSTC) circuits and supplementary motor area (SMA) might be central pathophysiological components of OCD [10-13]. The dorsolateral and dorsomedial prefrontal cortex (DLPFC, DMPFC), orbitofrontal cortex (OFC) and anterior cingulate are also proposed to be involved.

Involvement of these regions shows that pathophysiology of OCD is heterogeneous, just like the symptoms and subtypes, but at the same time suggests this could be an important source of variability in efficacy of OCD conventional treatments. The neuromodulatory treatments with brain stimulation can purposefully modulate target regions in OCD. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique proposed as a promising method for treating brain diseases including OCD [14-16]. TMS alters neural activity and excitability of targeted brain regions [17, 18]. Repetitive application (i.e., rTMS) results in neuroplastic after-effects in respective target areas, and depending on the specific stimulation protocol the effects are inhibitory or excitatory [16, 19]. These neuroplastic effects are the main rationale behind clinical therapeutic effects of rTMS [16, 20].

Previous rTMS studies reported an average response rate of 35% in OCD patients, defined as a minimum of 25–40% reduction in post-treatment symptoms [14]. However, higher response rates and augmented efficacy were recently reported in patients with a more homogenous pathological profile, such as common pathophysiological deficits [9, 21, 22]. This implies a relevance of predictors and correlates of successful rTMS treatment in OCD, and accordingly the need for personalizing rTMS treatment based on the pathophysiological and clinical profiles of the patients [21]. In this line, recent reviews of rTMS studies show that the state-dependent modulation of rTMS is an additional parameter that may potentially affect rTMS effects [23] which can help to improve treatment outcome in patients who usually develop treatment-resistant illness subtypes. Moreover, different cortical regions have been stimulated in previous studies and showed mixed results [24-28] which remains the question of “which cortical regions to stimulate?” unanswered.

While specific stimulation parameters and neurobiological predictors of response to rTMS treatment has been investigated in OCD [9, 29], the importance of clinical and demographic factors for rTMS response has not been systematically explored yet. These factors, especially clinical predictors, play a potentially key role in accurately selecting patients for rTMS treatment. Findings from rTMS studies in other neuropsychiatric disorders suggest that specific symptoms, subtypes or psychological states can distinguish between respondents and non-respondents to rTMS. We recently investigated the clinical and demographic predictors of rTMS response in depressive disorders and found that cognitive-affective symptoms compared to somatic symptoms could significantly predict response to rTMS [30]. Another study found that nonresponders to rTMS treatment for depression had markedly higher baseline anhedonia symptoms [31]. Although recent studies tried to predict response to rTMS treatment based on electrophysiological measure [26], clinical predictors of response so far have not been explored in OCD patients.

In the present study, we investigated the efficacy of rTMS over two potentially involved cortical regions (i.e., SMA and DLPFC) in reducing OCD symptoms. More importantly, we aimed to identify potential clinical and demographic predictors, if any, that could distinguish between rTMS responders and nonresponders in OCD. Based on previous findings about the efficacy of rTMS in OCD patients [14], we expect to observe a response rate of 35%-55% based on the 30% reduction of the Y-BOCS baseline score criterion. With regard to clinical predictors of rTMS response, we performed a retrospective exploratory

analysis on responders and nonresponders with demographic (namely age, gender, marital status, and educational level) and clinical characteristics (using an item-by-item examination of the Yale-Brown Obsessive-Compulsive Screening (Y-BOCS) as potential predictors of response.

Methods

2.1.Study design

We retrospectively analysed the dataset from outpatients who received rTMS treatment from July 2015 to May 2017. Patients were referred to Atieh Clinical Neuroscience Center to receive rTMS treatment and at the center, patients were evaluated using a semi-structured interview, Y-BOCS, BAI, BDI-II and some relevant cognitive / behavioural tasks. All interviews were carried out by a psychiatry resident, and all diagnoses were confirmed by one of the authors using DSM 5 clinical descriptions and diagnostic guidelines

2.2.Participants

Sixty-five pharmaco-resistant OCD outpatients (Mean age = 32.25, *SD* = 10.23, 35 females) who met our inclusion criteria were included in this study. The OCD diagnosis was based on the Structural Clinical Interview by a licensed psychiatrist according to the DSM 5 diagnostic criteria, confirmed by patient scores on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [32]. The inclusion criteria were: (1) 18-65 years old, (2) current OCD diagnosis based on DSM-5 (3) moderate to severe OCD score on the Y-BOCS (scores 16 and higher) (4) response failure to previous or current use of medication/psychotherapy (response failure was defined as scores > 16 at Y-BOCS despite at least two SSRI trials of adequate dose and duration) and (5) stable medication maintenance (if taken) for 12 weeks before the interventions and unchanged during treatment (4-6 weeks) [9]. Exclusion criteria included previous treatment with electroconvulsive therapy, and presence or history of psychosis, substance abuse, suicide attempt and/or active suicide ideation, neurological disorder, epilepsy, seizures, and head injury or loss of consciousness. According to the safety criteria for rTMS [33], patients with potential contraindications to rTMS, including implanted devices, foreign metal bodies, cardiac arrhythmia, unstable medical conditions, or pregnancy, were also excluded from treatment. Forty-nine of the patients were taking selective serotonin reuptake inhibitors (SSRIs) during rTMS treatment and the remaining patients had a history of SSRI medication use. All patients provided written informed consent to treatment. Demographic and clinical characteristics of patients are summarized in Table 1.

2.3. rTMS treatment parameters

RTMS was administrated with a Neuro MS rTMS device (Neurosoft, Russia) using a 70-mm figure-of-8-shaped coil (air film coil). Active motor threshold (AMT) was defined as the minimum stimulus intensity that produced a liminal motor evoked response during contraction of the abductor policies brevis muscle (APB) at about 20 % maximum [34]. The patients received either (1) SMA rTMS, or 2) bilateral DLPFC rTMS. For the SMA rTMS, the coil was positioned over the SMA, which was localized via the 10–20 EEG

system, and defined as 15% of the distance between nasion and inion anterior to the vertex in the sagittal plane [35]. In the SMA-rTMS protocol, TMS was delivered at 120% of AMT. Stimulation frequency was 1-Hz, for 30 min, resulting in a total of 1800 pulses per session. Stimulation was performed once a day, 3 days per week for 7 weeks, resulting in 20 sessions (36,000 pulses over 20 sessions). In DLPFC rTMS, all patients received bilateral stimulation given previous studies that showed mixed effects of unilateral stimulation of rTMS [28]. In DLPFC rTMS, the position of the coil was 5 cm anterior along a parasagittal line from the site of optimum APB stimulation [36]. The coil was placed over the left or right DLPFC. For bilateral DLPFC rTMS, stimulation was delivered over the right and left DLPFC respectively. First, 15 min of 1-Hz stimulation trains at 120% AMT, resulting in a total of 900 pulses per session, was applied over the right DLPFC, resulting in a total of 18,000 pulses over 20 sessions. Left DLPFC was stimulated immediately afterwards by applying 10-Hz stimulation at 120% AMT for 60 stimulation trains of a duration of 5 s each, with 10 s inter-train interval, resulting in a total of 3000 pulses per session in 15 min (60,000 pulses over 20 sessions).

2.4.Clinical procedure

All patients underwent a baseline clinical assessment with the Y-BOCS, Beck Anxiety Inventory (BAI) [37] and Beck Depression Inventory (BDI-II) [38] one week before rTMS treatment (pre-treatment) and at the end of treatment after the 20th session of rTMS (post-treatment) (Fig. 2). Baseline symptom severity was defined as a score of 16 or higher on the Y-BOCS (Mean = 22.20, *SD* = 7.01), which is the cut-off criterion for moderate OCD (8-15 mild, 16-23 moderate, 24-31 severe, 32-40 extreme). Treatment response was defined as a reduction of at least 30% in the Y-BOCS total scores based on some previous studies [26, 39] and is suggested to represent relevant clinical improvement in some studies (i.e., improvement of Clinical Global Impression (CGI)). It is of note that 35% symptoms reductions are also used in other studies and seems to be more common [40] however, we kept 30% of reduction to keep more responders in the binary regression analysis.

2.5.Measures

Y-BOCS: The Y-BOCS is the most widely used clinician-rated interview for assessing OCD symptom severity with adequate psychometric characteristics (i.e., interrater reliability and predictive validity) [41]. It contains 10 items, and each item is rated from 0 (no symptoms) to 4 (extreme symptoms). The Y-BOCS is sensitive to change, and during-treatment score reductions are a valid indicator of outcome [41]. Therefore, the items can be used as clinical predictors to treatment response. Similar to previous rTMS studies that used the BDI-II items as clinical predictors of response to rTMS in depression [30], we used each item as a potential clinical predictor of response to rTMS treatment. The Y-BOCS items weigh obsessions and compulsions equally. Obsession items assess spent time on obsessions (item 1), interference (item 2) and distress (item 3) due to obsessive thoughts, resistance against obsessions (item 4) and degree of control over obsessive thoughts (item 5). Items 6 to 10 assess respective variables (i.e., spent time, interference, distress, resistance, and degree of control) for compulsions respectively.

BAI & BDI-II: Both BAI and BDI-II consist of 21 items with a Likert scale ranging from 0 to 3 and raw scores ranging from 0 to 63 and are indicative for the presence of an anxiety or depression state. The BAI is well suited to monitor anxiety treatment outcome [42], and the obtained anxiety state is correlated with OCD symptoms [43, 44]. Similarly, the BDI-II scores are associated with OCD symptoms [44], which is not surprising due to the fact that around one-third of OCD patients suffer from comorbid depression [45]. Both measures have adequate psychometric properties.

2.6.Statistical analysis

Data analyses were conducted using the statistical package SPSS for Windows, version 24.0 (IBM, SPSS, Inc., Chicago, IL). In order to examine effectiveness of rTMS, a mixed model analysis of variance (ANOVA) was conducted with protocol (DLPFC rTMS vs. SMA rTMS) as the between-subject factors and time (pre-intervention vs. post-intervention). Mauchly's test was used to evaluate the sphericity of the data before performing the repeated measures ANOVA and in case that the assumption of sphericity was violated, the degrees of freedom were corrected using the Greenhouse–Geisser estimates of sphericity. The normality and homogeneity of the data were confirmed by the Shapiro-Wilk and Levin tests, respectively. For identifying demographic and clinical predictors of response to rTMS treatment in OCD patients, we split the participants to "responders" and "nonresponders" and conducted a binary logistic regression with "stepwise forward" selection of variables due to a large set of potential independent variables. The model was run in 2 steps in both analyses. Independent variables were age, gender, education, marital status (as demographic variables), all 10 items of the Y-BOCS that are assumed to measure different OCD symptoms. We ran the regression analysis separately on the Y-BOCS predictors in order not to increase number of predictors depending on our sample size as suggested [46]. To diagnose multicollinearity, we used the linear regression procedure and also calculated the correlation matrix among the predictor variables. A significance level of $p < 0.05$ was used for all statistical comparisons.

2.7.Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

3.1.Data overview

RTMS treatment was well-tolerated by most patients and no severe adverse effects were reported. Except for an occasional headache and dizziness, which usually disappeared spontaneously within 1–2 days the participants did not report side effects. Thirty patients (46.2%) had at least a 30% reduction in their Y-BOCS scores after 20 sessions of rTMS, the remaining patients (53.8%) were defined as non-responders to rTMS treatment. Specifically, in patients that underwent SMA rTMS, 16 out of 38 (42.1%) responded to rTMS treatment, which is equivalent to 53.3% of all responders. From the patients who underwent the bilateral DLPFC protocol, 14 out of 27 (51.9%) responded to the rTMS treatment, which is equivalent to

46.7% of all responders. The mean and standard deviation of patient scores based on their response and protocol they received on the Y-BOCS, BAI, and BDI-II before and after treatment are displayed in Table 2 and Fig 1.

3.2.Effectiveness of rTMS

The repeated measures ANOVA revealed a significant main effect of time on Y-BOCS scores in all participants ($F_{(1,63)}$ = 53.51, p < 0.01, η_p^2 = 0.46), indicating a significant reduction OCD symptoms after 20 sessions. However, no significant main effect of protocol ($F_{(1,63)}$ = 1.71, p < 0.19, η_p^2 = 0.02) or interaction effect of time × protocol ($F_{(1,63)}$ = 0.06, p < 0.80, η_p^2 = 0.01) were found indicating that rTMS efficacy was not dependent to the type of protocol (i.e., SMA vs DLPFC rTMS) applied. Bonferroni-corrected post hoc t-tests showed significant differences in the Y-BOCS scores after the intervention (t = 7.43, p < 0.01). With regard to anxiety and depressive states, ANOVA results showed a significant main effect of time on BAI ($F_{(1,63)}$ = 34.90, p < 0.01, η_p^2 = 0.357), and BDI-II scores ($F_{(1,63)}$ = 19.97, p < 0.01, η_p^2 = 0.241) indicating improving effects of rTMS in reducing anxiety and depressive symptoms. Again, the Bonferroni-corrected post hoc t-tests showed significant differences in the BAI (t = 5.83, p < 0.01) and BDI-II (t = 4.57, p < 0.01) scores after the intervention. No significant interaction of time × protocol or main effect of protocol were found in BAI scores ($F_{(1,63)}$ = 0.94, p < 0.33, η_p^2 = 0.015; $F_{(1,63)}$ = 0.43, p < 0.51, η_p^2 = 0.007) and depressive states measured by the BDI-II ($F_{(1,63)}$ = 0.01, p < 0.99, η_p^2 = 0.001; $F_{(1,63)}$ = 1.01, p < 0.32, η_p^2 = 0.016) (See Table 3).

3.3.Predictors of rTMS treatment

We conducted a binary logistic regression to identify demographic and clinical predictors of rTMS response in responders and non-responders. The overall model was statistically significant ($\chi 2$ = 27.74, p < 0.01, df = 2) indicating that clinical predictors could significantly distinguish non-responders from responders to rTMS treatment. Nagelkerke's R^2 of 0.46 indicates a relatively moderate relationship between predictors and rTMS response indicating that the model explained 46% of the variance of rTMS response in OCD patients. Prediction success was 82.9% (29 of 35) and 73.3% (22 of 30) for non-responders and responders respectively. The Wald criterion revealed items 2 (interference due to obsessive thought) and 9 (resistance against compulsions) of the Y-BOCS as the two most significant clinical predictors of rTMS treatment response in OCD. These items were successful in predicting non-responders to rTMS rather than responders. In other words, it was shown that 1-unit increase in response to items 2 and 9, would increase the risk of *not responding* to rTMS treatment 3.8 and 2.4 times (Odds ratio) respectively (Table 4). The intercept of -3.3.1 provides estimate for being in the reference group (i.e., responders) and since it has negative value it shows that higher scores in items 2 and 9 is associated with decreased probability of being a responder. No demographic factor, including age (p = 0.83), gender (p = 0.23), educational level (p = 0.11) and marital status (p = 0.79) as well as medication state (p = 0.86), significantly predicted response to rTMS in OCD patients.

Discussion

In this retrospective study, we reported the efficacy of rTMS in 65 OCD outpatients. A significant reduction in OCD symptoms and anxiety / depressive symptomatology were observed after 20 sessions of rTMS in the total group. 46.2% of the patients responded to rTMS treatment (based on the criterion of at least a 30% reduction of Y-BOCS baseline scores), although a significant reduction in OCD symptoms was observed in the whole patient group, including non-responders (less than 30% symptom reduction). No significant difference between the protocols (i.e., bilateral DLPFC vs. SMA rTMS) in the observed effects was found. Regarding the predictors of rTMS response, no demographic predictor (i.e., age, gender, marital status) could significantly predict response to rTMS in OCD. However, items 2 and 9 of the Y-BOCS (i.e., “interference due to obsessive thought” and “resistance against compulsions”) were the most significant clinical predictors of response to rTMS treatment, especially in the non-responder group. In other words, higher scores in these two items were associated with reduced clinical response to rTMS.

The response rate to rTMS in our OCD sample is in line with previous studies. The first meta-analysis in the field included 10 randomized controlled rTMS studies (with ≥25–40% reduction in Y-BOCS scores) and reported 35% response rate in 120 OCD patients that received rTMS [14]. Other recent studies reported a response rate of 40%-55% based on the 30% reduction of Y-BOCS baseline score criterion [24-27]. In all these studies, rTMS was applied over DLPFC or SMA / pre-SMA except for [26] that targeted medial PFC. Another recent meta-analysis showed that the therapeutic outcome of rTMS is not significantly different in the DLPFC vs SMA protocols, which was confirmed in our study too [29]. That said, a recent rTMS study in OCD patients targeted the dorsomedial PFC (DMPFC) and reported success rate of 50% with ≥50% reduction in post-treatment Y-BOCS scores, specifically in those OCD patients with hyperconnectivity of fronto-striatal circuits [9]. The additional benefit from DMPFC and DLPFC stimulation could be explained as indirect evidence of a possible modulation of the amygdala activity, which is known to be functionally connected to the dorsal and medial regions of PFC during processing of fearful-related and OCD-relevant stimuli respectively [47-49].

But more importantly, this suggests that response to rTMS treatment in OCD patients may depend on the pathophysiology of target region/s and whether involved regions are appropriately modulated. As mentioned earlier, OCD is a quite heterogeneous disorder not only at symptoms but also pathophysiology [4, 5, 50]. It might be the case that nonresponders to rTMS in our study have different subtypes with different pathophysiology in terms of the involved cortico-subcortical regions that were not adequately modulated with the DLPFC or SMA rTMS. The length and number of rTMS sessions can also affect the response with higher number of sessions providing more symptom reduction [24, 51] and our findings support this as we observed significant reduction of Y-BOCS scores even in non-responders.

Our findings about demographic and clinical predictors of rTMS response showed no significant demographic predictor (i.e., age, gender, marital status). This is in line with a recent study that found no correlation between baseline psychometric factors, including age, and rTMS treatment outcome [9], although age seems to be a predictor of rTMS treatment response in depression [52-55]. However, our

model showed that items 2 and 9 of the Y-BOCS, and respective symptoms, significantly predict response to rTMS treatment in OCD. These items were “interference due to obsessive thoughts” and “against compulsion”. Our analysis show that those OCD patients with higher scores in these 2 items, especially “interference due to obsessive thoughts”, were more likely to fail to respond to rTMS treatment.

It is notable here that the predictive ability of “interference due to obsessions” was almost 1.5 times higher than the “compulsion resistance”. The importance of this symptom, as the most significant predictor of rTMS treatment response has clinical implications. First of all, this can suggest that the symptom represented by this item might be more important for response failure to rTMS treatment. Patients with higher levels of OCD symptoms have more intrusive thoughts and experience greater overall difficulty due to obsession interference [27, 56]. This is in line with recent findings showing that obsessions are important in determining treatment response, and should be primarily targeted in interventions [57]. In accordance, our findings implicate that lower levels of obsessive symptoms and fewer interferences of intrusive thoughts, rather than overall OCD symptoms, can predict positive response to rTMS treatment. In this line are results of a recent rTMS study on treatment-resistant OCD patients which showed that improvement of the Y-BOCS score was mainly due to the improvement of compulsions and not obsessive thoughts [27]. Secondly, the relationship between intrusive thoughts and development and maintenance of OCD symptoms [58] might also explain why stronger and more intrusive obsessions (item 2) hinder response to rTMS treatment.

But in addition to “interference due to obsessive thoughts” (item 2), item 9 was the second significant predictor of response to rTMS in OCD patients. This item is a measure of resistance against compulsions (i.e., being yielded to compulsions) and it is suggested that greater score in this item is interpreted as representation more severe symptoms [59-61]. This item is suggested to be related to “resistance factor” rather than “obsession” or “compulsion” factors and unlike items related to obsession and compulsion, does not significantly change after pharmacological treatment [59, 62]. Similarly, here we found that higher scores in this item predict response failure to rTMS treatment which should be taken into account in rTMS treatment decision for refractory OCD patients.

The major implication of our findings is that application of rTMS protocols in OCD patients could be adapted to patients’ symptoms. According to what we found, OCD patients with more obsession interference and compulsion resistance might benefit more from protocols that are optimized to have stronger impacts on interference or inhibition. An alternative option would be other potentially effective treatments in OCD nonresponders to rTMS treatment. For example, it is shown that resistance symptoms (e.g., item 9) are not moderated by pharmacological treatment alone whereas they significantly decline in response to cognitive-behavioral intervention [62]. This may suggest using alternative treatment options in OCD non-responders to rTMS. Therefore, treatment strategies that are focused on improving maladaptive appraisal and control strategies in response to intrusive thoughts, which are associated with greater distress and interference [63-67], might be valuable first-line treatments in those OCD patients who fail to respond to rTMS. However, personalizing and adapting stimulation protocols [23] should not only

include identifying clinical and non-clinical predictors but also stimulation parameters which need to be more studied in the future.

It is important to note that findings are preliminary and should be interpreted with cautions considering the following limitations. The major limitation in our analysis is the retrospective study design. This was due to the retrospective nature of the study but on the other hand, our analysis benefits from the ecological validity and provided us with a realistic picture about the clinical application of rTMS in clinical settings. Secondly, our control condition was limited to baseline-control and lack sham condition. This was again due to retrospective nature of the study that was conducted on outpatients who received real rTMS treatment. The next limitation concerns the required sample size for reliable prediction in linear regression. Although the sample size was large enough for investigating the efficacy of rTMS, it may not be adequate for binary regression analysis and thus results should be interpreted with caution. Multi-center studies with a larger sample are needed to provide additional insight into demographic and clinical predictors of response to rTMS in OCD. In addition to these, our sample was heterogeneous in terms of add-on pharmacotherapy. Although we kept the medication dosage constant 12 weeks before the experiment and throughout the intervention (4-6 weeks) to minimize potential confounding and interference and this factor did not predict response status, it should be controlled directly in future studies as this might be a potential source of variability in rTMS effects.

Conclusions

In sum our findings suggest using a more adaptive and personalized protocol by identifying potential clinical factors (i.e., OCD subtypes, symptom-related pathophysiology, comorbidity with other disorders) and non-clinical predictors. Specifically, those patients with more severe intrusive thoughts and less control over compulsive behaviors might not be good candidates for receiving DLPFC and/ or SMA rTMS treatment. Instead, interventions that are primarily based on improving control strategies in response to intrusive thoughts, such as suppression and neutralization, which are ingredients of behavioral and cognitive interventions, might be more effective in medication-resistant and rTMS-resistant OCD patients.

Abbreviations

rTMS = repetitive transcranial magnetic stimulation

OCD = obsessive-compulsive disorder

SMA = supplementary motor area

DLPFC = dorsolateral prefrontal cortex

Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

BAI = Beck Anxiety Inventory

BDI-II = Beck Depression Inventory

AMT = Active motor threshold

APB = abductor policies brevis muscle

Declarations

Ethics approval and consent to participate

The protocol was conducted in accordance with the latest version of the Declaration of Helsinki and was approved by the Institutional Review Board and ethical committee at the Atieh Clinical Neuroscience Centre and University of Tehran.

Consent for publication

“Not applicable”

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest statement

MAN is a member of the Scientific Advisory Board of Neuroelectrics. All other authors declare no competing interests.

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None

Authors’ contributions

RR, RK & MAS conceived the study. AJ, A-S M, HR & MAT collected the data. MAS analyzed and interpreted the data. MAS wrote the first draft. MAN, CV, M-F K, NJ revised and reviewed. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic information of participants

Variable	Group	n	Response (≥30%)		*p*-value
			Yes	No	
Sample size (*n*)		65	30	35	
Comorbidity (*n*)		34	12	22	0.06
On medication (n)		49	22	27	0.55
Protocol	SMA rTMS	38	16	22	0.30
	DLPFC rTMS	27	14	13	
Age	Mean (SD)	32.25 (10.23)	32.67 (9.44)	31.89 (10.99)	0.76
Gender	Male	30	14	16	0.56
	Female	35	16	19	
Education	Diploma or lower	24	10	14	0.65
	Associate degree	7	3	4	
	Bachelor degree	22	11	11	
	Masters degree	6	2	4	
	Not reported	6	4	2	
Marital status	Single	26	10	16	0.71
	Married	33	17	16	
	Divorced or separated	6	3	3	

Note: SMA = Supplementary motor area; rTMS = repetitive transcranial magnetic stimulation; DLPFC = dorsolateral prefrontal cortex; SD = Standard Deviation. Between group differences in demographic variables were explored using chi-square analysis or Fisher's exact test for categorical variables and t tests for continuous variables

Table 2. Means and *SD*s of OCD, anxiety and depressive scores before and after rTMS treatment based on the response (responders vs nonresponders) and protocol (SMA rTMS vs DLPFC rTMS).

Measure	Response	pre-intervention		post-intervention		Pre vs post
		M (*SD*)	*t (sig)*	*M* (*SD*)	*t (sig)*	*t (sig)*
Y-BOCS	responders	22.90 (6.94)	-0.32 (0.75)	12.73 (6.01)	-5.38 (**0.01**)	12.39 **(0.001)**
	non-responders	22.62 (6.50)		21.02 (5.97)		2.35 **(0.025)**
	total	22.75 (6.66)		17.20 (7.25)		7.43 **(0.001)**
	SMA rTMS	23.52 (7.37)	1.11 (0.27)	18.13 (7.95)	1.23 (0.22)	3.06 (**0.003**)
	DLPFC rTMS	21.66 (5.44)		15.88 (6.04)		3.69 (**0.001**)
BAI	responders	27 (9.72)	0.60 (0.54)	15.13 (7.51)	-0.71 (0.47)	5.84 **(0.001)**
	non-responders	24.97 (12.06)		18.37 (10.65)		2.95 (**0.005**)
	total	25.91 (11.01)		16.87 (9.41)		5.83 **(0.001)**
	SMA rTMS	24.71 (10.15)	-1.04 (0.30)	16.94 (9.95)	0.07 (0.94)	3.36 (**0.001**)
	DLPFC rTMS	27.59 (12.10)		16.77 (8.77)		3.76 (**0.001**)
BDI-II	responders	22.50 (9.78)	-0.20 (0.84)	16.43 (9.93)	-0.12 (0.91)	3.17 **(0.003)**
	non-responders	22.77 (8.32)		17.28 (9.16)		3.25 (**0.002**)
	total	22.64 (8.95)		16.89 (9.46)		4.57 **(0.001)**
	SMA rTMS	21.84 (9.86)	-0.85 (0.39)	16.07 (9.28)	-82 (0.41)	2.62 (**0.010**)
	DLPFC rTMS	23.77 (7.54)		18.03 (9.77)		2.42 (**0.019**)

Y-BOCS = Yale-Brown Obsessive-Compulsive Screening; BAI = Beck Anxiety Inventoy; BDI-II = Beck Depession Inventoy; M = Mean; SD = Standard Deviation. Significant results are highlighted ($p \leq 0.05$) in **bold**

Table 3: Results of the Mixed model ANOVAs for effects of protocol (SMA vs DLPFC rTMS) and time (pre-intervention, post-intervention) on OCD, anxiety and depressive symptoms in OCD patients.

Measure	Source	df	Mean square	F	p-value	partial eta2
Y-BOCS	Time	1,63	958.15	53.51	**0.001**	0.46
	Protocol	1,63	132.82	1.70	0.197	0.01
	Time*protocol	1,63	1.15	0.06	0.803	0.05
BAI	Time	1,63	2727.96	34.90	**0.001**	0.36
	Protocol	1,63	58.06	0.43	0.511	0.18
	Time*protocol	1,63	73.49	0.94	0.336	0.01
BDI-II	Time	1,63	1044.46	19.97	**0.001**	0.24
	Protocol	1,63	119.65	1.01	0.318	0.02
	Time*protocol	1,63	0.004	0.01	0.993	0.01

Y-BOCS = Yale-Brown Obsessive-Compulsive Screening; BAI = Beck Anxiety Inventoy; BDI-II = Beck Depession Inventoy. Significant results are highlighted ($p \leq 0.05$) in **bold**

Table 4. Binary logistic regression analysis: analysis of significant clinical predictors (using Y-BOCS items) of response to rTMS treatment.

Predictors *Nagelkerke R^2 46%*	Predicted group	β	Wald	df	p	Odd ratio (e β)	95% CI	
							Lower	Upper
	Non-responders							
Interference due to obsessive thoughts (2)		1.34	9.89	1	**0.01**	3.83	1.66	8.86
Resistance against compulsions (9)		0.86	7.41	1	**0.01**	2.38	1.27	4.45
Constant		-3.31	13.06	1	0.01	0.03		
Time occupied by obsession (1)					0.10			
Distress associated with obsessions (3)					0.35			
Resistance against obsessions (4)					0.76			
Control over obsessions (5)					0.41			
Time spent on compulsions (6)					0.67			
Interference due to compulsions (7)					0.75			
Distress associated with compulsions (8)					0.90			
Control over compulsions (10)					0.73			

Predicted group = the group coded with value 1 in binay regression analysis; Significant results are highlighted ($p \leq 0.05$) in bold.

Figures

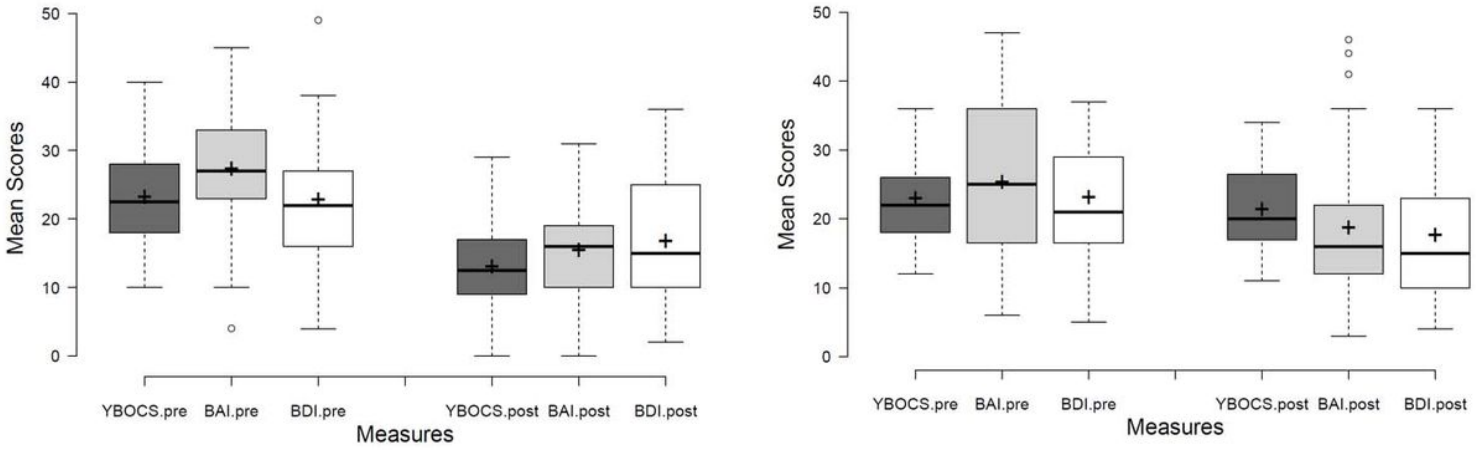

Figure 1

Mean score of responders (left) and nonresponders (right) to rTMS in the Y-BOCS, BAI, and BDI-II before and after rTMS treatment. Note: Y-BOCS = Yale-Brown Obsessive-Compulsive Screening; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory; pre = pre-intervention; post = post intervention; Error bars indicate 95% confidence intervals; Boxes indicate the interquartile range that contains 50% of values (range from the 25th to the 75th percentile)

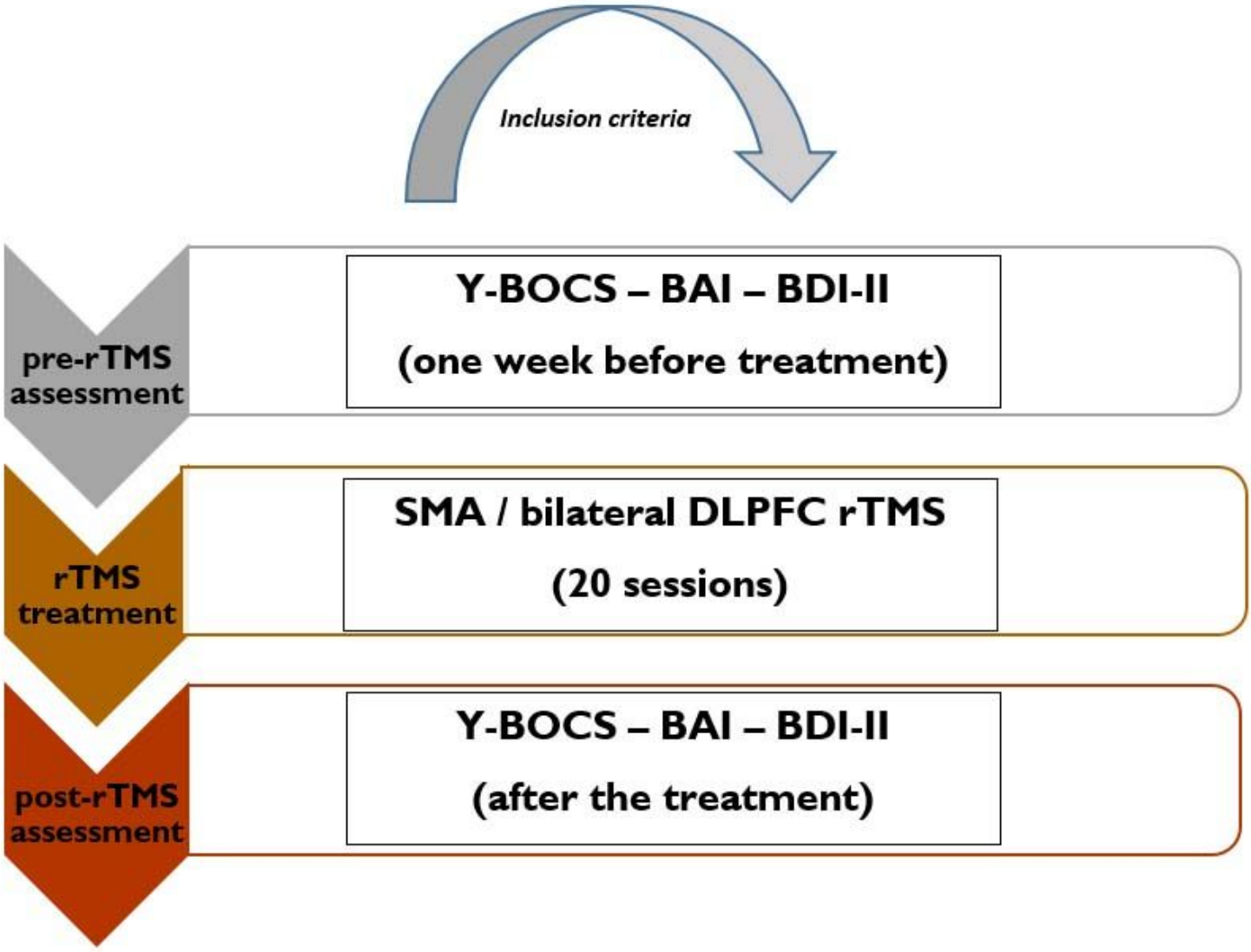

Figure 2

Procedure of rTMS treatment. Note: Y-BOCS = Yale-Brown Obsessive-Compulsive Screening; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory; SAM = supplementary motor area; DLPFC = dorsolateral prefrontal cortex.