Efficacy and clinical predictors of response to rTMS treatment in pharmacoresistant 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 may 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 pharamcoresistant OCD outpatients recruited for the rTMS treatment from July 2015 to May 2017. Patients received either SMA rTMS or bilateral DLPFC rTMS based on their symptoms and OCD symptoms and depression/anxiety states were measured at baseline (before the 1st session) and after the 20th session of rTMS. Additionally, we performed a binary logistic regression analysis on the demographic variables and clinical variables based on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) items and factors to investigate demographic and clinical predictors for rTMS response in the rTMS responders and non-responders. Results: Patients’ scores in Y-BOCS and Beck anxiety/depression inventories were significantly decreased following rTMS treatment. 46.2% of all patients responded to rTMS, based on at least a 30% reduction in Y-BOCS scores. The stimulation target (DLPFC vs. SMA) did not significantly differ in rTMS efficacy. No significant demographic predictors were found. “Interference due to obsessions”, “resistance against compulsions” and “disturbance” factor could significantly predict response failure to rTMS. Conclusions: Patients with less intrusive/interfering thoughts and low scores in the “disturbance” factor 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. Interpretation of rTMS efficacy should be cautious due to the Lack of sham condition.
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 (obessions), 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 outcomes 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 measures [26], clinical predictors of response so far have not been explored in OCD patients.

In the present study, we aimed to investigate 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 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 aim to see if there are any clinical (i.e., OCD symptoms) or demographic variables that can predict treatment response to rTMS in OCD-patients.

Methods

2.1 Study design

We retrospectively analyzed the dataset from pharamco-resistant OCD outpatients who received rTMS treatment from July 2015 to May 2017. Our study is not, however, a retrospective medical record study. Patients were referred to Atieh Clinical Neuroscience Center in Tehran, Iran to receive rTMS treatment. The center admits patients with psychiatric disorders (e.g. depression, OCD), neurological disorders (e.g. stroke, dementia) and pediatric neurodevelopmental disorders (e.g. attention-deficit hyperactivity disorder, autism, learning disabilities). Typical interventions include non-invasive brain stimulation, pharmacological, behavioural and psychological interventions.

2.2 Participants

Sixty-five pharmaco-resistant OCD outpatients (Mean age = 32.25, \(SD = 10.23\), 35 females) who completed the treatment were included in this study. A priori sample size
calculation based on power analysis showed that based on medium effect size (f=0.5), a critical p-value of 0.05, a power of 0.95, the required sample size for or study design is 42 and we achieved a power of 0.99. 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 regimen 12 weeks before the interventions and unchanged during the 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. 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. Most of the patients had no history of psychotherapy. All patients provided written informed consent to treatment. Demographic and clinical characteristics of patients are summarized in Tables 1 and 2.

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 active
contraction of the abductor pollicis brevis muscle (APB) (at about 20% maximum contraction) [34]. Motor threshold determination was based on visual inspection of hand movement. 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 afterward 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). Participants received SMA or DLPFC rTMS based on their symptoms type and those with higher levels of anxiety and depressive state received
DLPFC rTMS. 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 a relevant clinical improvement in some studies (i.e., improvement of Clinical Global Impression (CGI)). It is of note that 35% of symptom reductions are also used in other studies and seem to be more common [40] however, we kept 30% of reduction to keep more responders in the binary regression analysis. 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 local university and Atieh Clinical Neuroscience Centre.

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., inter-rater 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 outcomes [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 the effectiveness of rTMS, 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 “non-responders” and conducted a binary logistic regression. To control for potential confounding variables, we added them into the model as the model can itself adjust for potential co-founders sing adjusted odds-ratio [46]. The model goodness of fit was done using the Hosmer-Lemeshaw statistic, which also adjusts for potential covariates, and the variable section was based on the “stepwise forward” strategy 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 [47]. To diagnose multicollinearity, we used the linear regression procedure and entered all covariates in the model to diagnose potential multicollinearity. 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 Participants characteristics

The mean age of responders (N=30, 16 females) and nonresponders (N=35, 19 females) were 32.67 (9.44) and 31.89 (10.99) respectively. There was no significant difference between groups in demographic variables (e.g. age, gender, education, marital status) as well as comorbidity rate, medication use and applied protocol (i.e., SMA vs DLPFC rTMS) (Table 1) and thus we did not enter them as a potential covariate. Moreover, we also compared the same demographic variables, treatment response, and baseline OCD, anxiety and depressive scores in the groups based on the protocol they received (i.e., SMA vs DLPFC rTMS). Results show so significant between-group differences in demographics and baseline measurements (Table 2).

3.2 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 3 and Fig 1.

3.3 Effectiveness of rTMS

The repeated measures ANOVA revealed a significant main effect of time on Y-BOCS scores in all participants ($F_{(1,63)} = 53.51, p < 0.01, \eta^2_p = 0.46$), indicating a significant reduction OCD symptoms after 20 sessions. However, no significant main effect of protocol ($F_{(1,63)} = 1.71, p < 0.19, \eta^2_p = 0.02$) or interaction effect of time $\times$ protocol ($F_{(1,63)} = 0.06, p < 0.80, \eta^2_p = 0.01$) 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 paired t-tests for pre-post values 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 ($F_{(1,63)} = 34.90, p < 0.01, \eta^2_p = 0.357$), and BDI-II scores ($F_{(1,63)} = 19.97, p < 0.01, \eta^2_p = 0.241$) indicating improving effects of rTMS in reducing anxiety and depressive symptoms. Again, the Bonferroni-corrected post hoc t-tests for pre-post values 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 $\times$ protocol or main effect of protocol were found in BAI scores ($F_{(1,63)} = 0.94, p < 0.33, \eta^2_p = 0.015; F_{(1,63)} = 0.43, p < 0.51, \eta^2_p = 0.007$) and
depressive states measured by the BDI-II ($F_{(1,63)} = 0.01, p < 0.99, \eta^2_p = 0.001$; $F_{(1,63)} = 1.01, p < 0.32, \eta^2_p = 0.016$) (See Table 4).

3.4 Predictors of rTMS treatment

Results of multicollinearity analysis showed the variance inflation factor (VIF) of higher than 3 for only 2 dependent variables, however, the VIF around 10 is indicative of high multicollinearity [48]. The VIFs for items 1-9 are 2.60, 2.07, 3.05, 1.35, 2.98, 2.86, 3.16, 2.61, and 2.32 respectively. 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 and 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 5). No demographic factor, including age ($p = 0.83$), gender ($p = 0.23$), and educational level ($p = 0.11$) as well as other clinical variables such as comorbidity ($p = 0.81$) and medication use ($p = 0.86$), significantly predicted response to rTMS in OCD patients.

We also did a similar binary regression analysis on factors extracted the Y-BOCS items
based on the three-factor model [49], two-factor model [50], and the three-dimensional model [51]. We entered all 7 factors into the model. The overall model was statistically significant (χ² = 23.79, p < 0.01, df = 1) with a Nagelkerke’s R² of 0.41 and prediction success of 74.3% (26 of 35) and 76.7% (23 of 30) for non-responders and responders respectively. The Wald criterion revealed the “disturbance” factor (items, 2,3,7,8) as the only significant clinical factor extracted from the Y-BOCS in predicting rTMS response in OCD.

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 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 a 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 [52-54].

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, 55]. 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, 56] and our findings may support this as we observed a significant reduction of Y-BOCS scores even in non-responders. Lastly, we should nevertheless note that although we had baseline-control, due to lack of sham condition our finding (about efficacy) should be interpreted with caution.

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 [57-60]. 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 shows 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. Results of the next model on Y-BOCS factors showed that the “disturbance” factor which is indicative of distress and interference [50] was the only significant factor in predicting rTMS response which is related to interference symptoms, including item 2 of the Y-BOCS.

It is notable here that the predictive ability of “interference due to obsessions” was almost 1.5 times higher than the “compulsion resistance”. In this line, the “disturbance” factor the only significant factor from the Y- Y-BOCS which again indicates the importance of interference-related symptoms in rTMS treatment response. 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, 61]. This is in line with recent findings showing that obsessions are important in determining treatment response, and should be primarily targeted in interventions [62]. 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 [63] 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 [49, 50, 64]. 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 [49, 51].

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 [51]. 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 [65-69], 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 that need to be more studied in the future.

It is important to note that findings are preliminary and should be interpreted with caution considering the following limitations. The major limitation of 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 lacked a sham condition which requires a conservative interpretation of results. This was again due to the retrospective nature of the study that was conducted on outpatients who received real rTMS treatment. Unblinded assessment and using multiple raters which could be a potential source of inter-rater variability among the raters are other limitations of our work. 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, more distress 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 pollicis 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                      | Category         | n   | Response (≥30%) |
|------------------------------|------------------|-----|-----------------|
|                              |                  |     | Yes            | No        |
| Sample size (n)              |                  | 65  | 30             | 35        |
| Comorbidity (yes)            |                  | 34  | 12             | 22        |
| On medication (yes)          |                  | 51  | 16             | 22        |
| Protocol                     |                  |     |                |           |
| SMA rTMS                     |                  | 38  | 14             | 16        |
| DLPFC rTMS                   |                  | 27  | 16             | 19        |
| Age                          | Mean (SD)        | 32.25 (10.23) | 14       | 16        |
| Gender                       |                  |     |                |           |
| Male                         |                  | 30  | 10             | 14        |
| Female                       |                  | 35  | 3              | 4         |
| Education                    |                  |     |                |           |
| Diploma or lower             |                  | 24  | 4              |           |
| Associate degree             |                  | 7   | 10             | 16        |
| Bachelor degree              |                  | 22  | 17             | 16        |
| Masters degree               |                  | 6   | 3              | 3         |
| Not reported                 |                  | 6   |                |           |
| Marital status               |                  |     |                |           |
| Single                       |                  | 26  |                |           |
| Married                      |                  | 33  |                |           |
| Divorced or separated        |                  | 6   |                |           |

Note: SMA = Supplementary motor area; rTMS = repetitive transcranial magnetic stimulation; DLPFC = dorsolateral prefrontal cortex; SD = Standard Deviation. Between group (responders vs non-responders) 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. Group (SMA vs DLPFC rTMS) characteristics
Table 3. Means and SDs 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).

Note: SMA = Supplementary motor area; rTMS = repetitive transcranial magnetic stimulation; DLPFC = dorsolateral prefrontal cortex; SD = Standard Deviation. Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory; Group differences based on the applied protocol (SMA vs DLPFC rTMS) in demographic variables were explored using chi-square analysis or Fisher's exact test for categorical variables and t-tests for continuous variables.
| Measure  | Source  | df | Mean square | F     | p-value |
|---------|---------|----|-------------|-------|---------|
| Y-BOCS  | Time    | 1,63 | 958.15      | 53.51 | 0.001   |
|         | Protocol | 1,63 | 132.82      | 1.70  | 0.197   |
|         | Time*protocol | 1,63 | 1.15        | 0.06  | 0.803   |
| BAI     | Time    | 1,63 | 2727.96     | 34.90 | 0.001   |
|         | Protocol | 1,63 | 58.06       | 0.43  | 0.511   |
|         | Time*protocol | 1,63 | 73.49       | 0.94  | 0.336   |
| BDI-II  | Time    | 1,63 | 1044.46     | 19.97 | 0.001   |
|         | Protocol | 1,63 | 119.65      | 1.01  | 0.318   |
|         | Time*protocol | 1,63 | 0.004       | 0.01  | 0.993   |

Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory; M = Mean; SD = Standard Deviation. Significant results are highlighted (p ≤ 0.05) in **bold**.
Significant results are highlighted (p ≤ 0.05) in **bold**

Table 5. Binary logistic regression analysis: analysis of significant clinical predictors (using Y-BOCS items) of response to rTMS treatment.

| Predictors                              | mean item score in NR (R) | Predicted group | β     | Wald  | df | p      | Odd ratio (e^β) |
|-----------------------------------------|---------------------------|-----------------|-------|-------|----|--------|-----------------|
| **Nagelkerke R^2 46%**                  |                           |                 |       |       |    |        |                 |
| Interference due to obsessive thoughts  | 2.51 (2.17)               | Non-responders  | 1.34  | 9.89  | 1  | 0.002  | 3.13            |
| Resistance against compulsions (9)      | 1.83 (1.90)               |                 | 0.86  | 7.41  | 1  | 0.006  | 2.38            |
| Constant                                |                           |                 | -3.31 | 13.06 | 1  | 0.01   | 0.03            |
| Time occupied by obsession (1)          | 2.69 (2.67)               |                 |       |       |    |        | 0.10            |
| Distress associated with obsessions (3) | 2.66 (2.80)               |                 |       |       |    |        | 0.14            |
| Resistance against obsessions (4)       | 1.89 (1.90)               |                 |       |       |    |        | 0.29            |
| Control over obsessions (5)             | 2.63 (2.80)               |                 |       |       |    |        | 0.21            |
| Time spent on compulsions (6)           | 2.00 (1.93)               |                 |       |       |    |        | 0.68            |
| Interference due to compulsions (7)     | 1.94 (1.87)               |                 |       |       |    |        | 0.96            |
| Distress associated with compulsions (8)| 2.26 (2.37)               |                 |       |       |    |        | 0.81            |
| Control over compulsions (10)           | 2.34 (2.50)               |                 |       |       |    |        | 0.67            |
| Disturbance factor (items, 2,3,7,8)    | 8.51 (4.93)               |                 | 0.51  | 13.48 | 1  | 0.001  | 1.67            |
| Symptom severity factor (items 1,4,5,6,9,10) | 12.54 (7.80)         |                 |       |       |    |        | 0.09            |
| Resistance factor                       | 3.68 (2.30)               |                 |       |       |    | 0.19   |                 |
| Obsession severity factor (items 1-3,5) | 9.54 (6.13)               |                 |       |       |    | 0.15   |                 |
| Compulsion severity factor (items 6-8,10) | 7.82 (4.30)             |                 |       |       |    | 0.78   |                 |
Predicted group = the group coded with value 1 in binary regression analysis; NR = non-responders; R = responders;

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)
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.