Psychiatry Research 317 (2022) 114856

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Short communication

Use of right orbitofrontal repetitive transcranial magnetic stimulation (rTMS) augmentation for treatment-refractory obsessive-compulsive disorder with comorbid major depressive disorder

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ARTICLE INFO

Keywords:
Comorbid OCD-MDD
rTMS
Orbitofrontal cortex

ABSTRACT

We examined the safety and efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) of the right orbitofrontal cortex (OFC) in patients with refractory obsessive-compulsive disorder (OCD) and comorbid Major Depressive Disorder. All participants ($n = 26$) received excitatory stimulation of the left dorsolateral prefrontal cortex followed by inhibitory stimulation of bilateral supplementary motor area for 10 sessions. In 18 patients with poor early OCD response, treatment was augmented with OFC inhibitory stimulation after the tenth treatment session. Augmentation with OFC stimulation was well-tolerated, and associated with further alleviation of both OCD and depression symptoms, particularly in individuals with more severe illnesses.

1. Introduction

Obsessive-Compulsive Disorder (OCD) is commonly comorbid with depression: up to 70% of patients suffer depressive symptoms and 40% meet criteria for Major Depressive Disorder (MDD) (Ruscio et al., 2010; Sharma et al., 2021). Comorbid OCD-MDD has a poorer prognosis than either illness alone, and psychotherapeutic and pharmacological treatments for individuals with OCD-MDD are limited (Stein et al., 2019). Our group recently reported promising results in a preliminary study using a novel multi-locus repetitive Transcranial Magnetic Stimulation (rTMS) treatment protocol targeting the left dorsolateral prefrontal cortex (DLPFC) and bilateral supplementary motor area (SMA) in seven patients with refractory OCD-MDD (Tadayonnejad et al., 2020). The present open-label study extends our previous work to examine whether augmentation of the DLPFC+SMA protocol with inhibitory stimulation of right orbitofrontal cortex (OFC), which has been shown to have therapeutic benefits for OCD (Nauczyciel et al., 2014) and MDD (Feffer et al., 2018), is safe and effective for enhancing treatment outcome in comorbid subjects who have poor early response to DLPFC+SMA stimulation alone.

2. Methods

Twenty-six patients with refractory comorbid OCD-MDD consented and enrolled in this study (18 males, 8 females, mean age 32.4 ± 11.28, please see Fig. 1A for Inclusion/Exclusion criteria). The UCLA Institutional Review Board approved this retrospective analysis of de-identified data. The average duration of OCD and MDD conditions across patients was 15.2 ± 10.70 years and 11.5 ± 9.97 years, respectively. Subjects had previously tried on average 7 ± 2.6 different psychotropic medications (including SSRIs and antipsychotics) and 2 ± 1.0 courses of psychotherapy consisting of exposure and response prevention (the primary behavioral treatment option for OCD) and/or cognitive behavior therapy with suboptimal improvement. Patients had moderately severe average baseline OCD (mean Yale-Brown Obsessive Compulsive scale [Y-BOCS] score of 23.8 ± 7.1) (Goodman et al., 1989), severe depressive symptoms (mean Inventory of Depressive Symptomatology-Self-Report [IDS-SR] score of 42.4 ± 12.1) (Rush

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https://doi.org/10.1016/j.psychres.2022.114856
Received 28 March 2022; Received in revised form 10 September 2022; Accepted 18 September 2022
Available online 20 September 2022

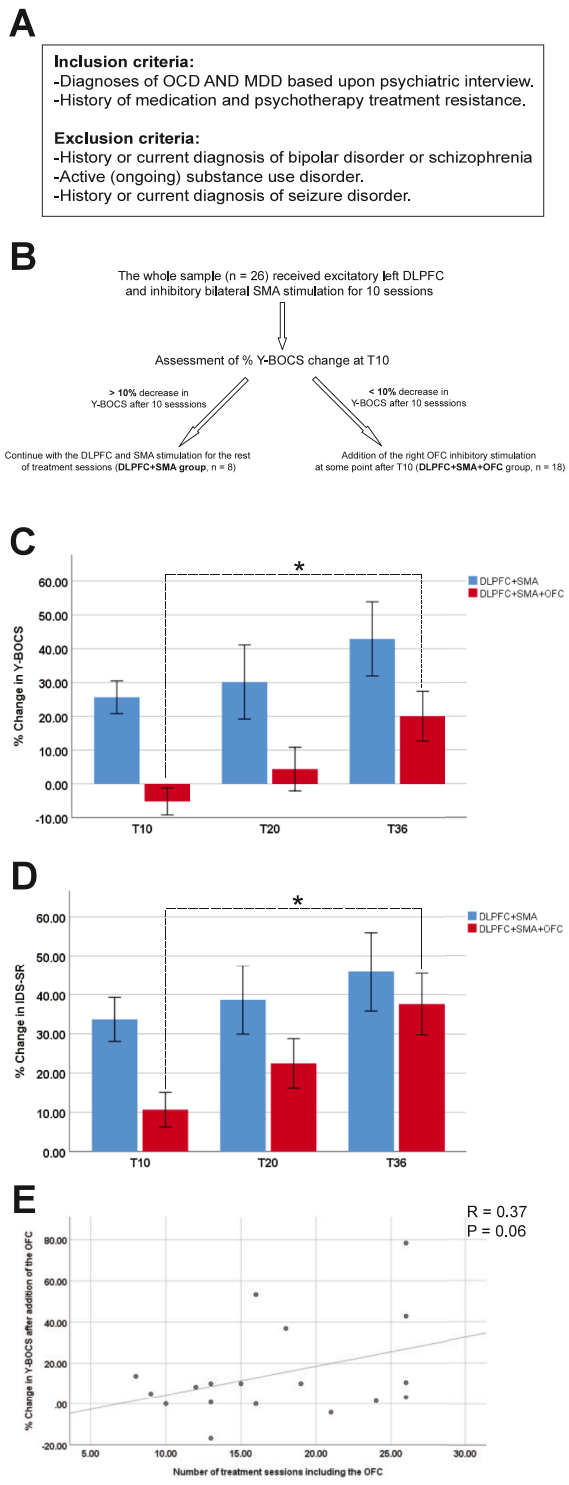

Fig. 1. (**A**) Main Inclusion\Exclusion criteria of the study. (**B**) Illustrative flowchart of the study design. (**C**) Graphs of the average percentage reduction in OCD symptom severity in terms of Y-BOCS score in DLPFC+SMA (*Blue*), DLPFC+SMA+OFC (*Red*) groups. (**D**) Graphs of the average percentage reduction in depression symptom severity in terms of IDS-SR score in DLPFC+SMA (*Blue*), DLPFC+SMA+OFC (*Red*) groups. (**E**) Correlation (at the trend level) between the number of sessions that include the OFC stimulation and the extra% change in Y-BOCS after the addition of OFC in the DLPFC+SMA+OFC group. T10: tenth session; T20: twentieth treatment session; T36: Thirty-sixth treatment session; Y-BOCS: Yale-Brown Obsessive Compulsive scale; IDS-SR: Inventory of Depressive Symptomatology-Self-Report.

et al., 1986), and severe depressive ruminative thinking (mean Ruminative Response Scale [RRS] of 61 ± 10.5) (Nolen-Hoeksema and Morrow, 1991).

All subjects received 10 initial sessions of 10 Hz excitatory rTMS (3000 pulses) ($N = 14$) or intermittent Theta Burst Stimulation (iTBS; 1800 pulses) ($N = 12$) over the left dorsolateral prefrontal cortex (DLPFC) at 120% MT followed by 1200 pulses of 1 Hz inhibitory rTMS over the bilateral supplementary motor area (SMA) at 130% MT (Mantovani et al., 2010). Using a measurement-based care paradigm (study flowchart in Fig. 1B), subjects were assessed after the first 10 treatments (T10) with those showing ≥ 10% improvement in their Y-BOCS continuing with the same protocol for another 26 sessions (DLPFC+SMA group, $n = 8$). For those subjects with < 10% improvement at T10, treatment was augmented with 1200 pulses 1 Hz inhibitory rTMS administered to right orbitofrontal cortex (OFC)(defined as the Fp2 electrode location from the International 10–20 system) delivered at 130% MT (DLPFC+SMA+OFC group, $n = 18$). Clinicians had the discretion to add OFC stimulation at treatment 11 or later. Please see the Supplementary Information file for more methodological details.

3. Results

Participants ($n = 26$) showed significant symptom improvement following 36 rTMS treatments, with a 28% decrease in OCD (Y-BOCS: baseline = 23.8 ± 7.1, T36 = 17.1 ± 8.4, $P = 0.003$) and a 41% decrease in depressive (IDS-SR on baseline = 42.4 ± 12.1, T36 = 25.1 ± 13.5, $P = 0.0001$) symptom severity. There were no significant adverse events during treatment and no subjects discontinued treatment before completing the full course of treatment.

After the initial 10 sessions during which only DLPFC+SMA stimulation was administered, subjects showed on average 4.3% and 18% decreases in OCD and depression symptom severity, respectively. All subjects with ≤ 10% Y-BOCS improvement at T10 ($n = 18$) received OFC augmentation for an average of 17 [± 6.2] sessions (DLPFC+SMA+OFC group). Baseline clinical (Y-BOCS and IDS-SR) and demographic (age, sex) characteristics were not significantly different between DLPFC+SMA and DLPFC+SMA+OFC groups.

The DLPFC+SMA+OFC group showed an average 20% reduction in Y-BOCS and a 37% reduction in IDS-SR scores following the full course of treatment. This group also showed a significant improvement in both OCD (%Y-BOCS at T10 = −5 ± 16.9 vs T36 = 20.0 ± 31.3, $P = 0.004$, Fig. 1C) and depression (%IDS-SR at T10 = 10.6 ± 18.7 vs T36 = 37.5 ± 33.2, $P = 0.007$, Fig. 1D) scores from T10 to T36.

Subjects with more than 10% Y-BOCS improvement at T10 ($n = 8$), showed 40% and 45% reductions in Y-BOCS and IDS-SR scores, respectively, after receiving 36 treatment sessions with only DLPFC+SMA. There was no statistically significant difference between treatment groups after 36 treatment sessions in the percent Y-BOCS ($P = 0.09$, Fig. 1C) or IDS-SR ($P = 0.54$, Fig. 1D) improvement (independent *t*-test).

There was a positive trend association between the number of treatment sessions that included OFC stimulation and greater improvement in Y-BOCS = ($R = 0.37$, $P = 0.06$, Fig. 1E). This effect was driven by 4/18 participants in whom the addition of the OFC stimulation site resulted in ~40–80% additional decrease in Y-BOCS. Interestingly, all those four subjects were female. A *post hoc* analysis showed that subjects with the most robust response to OFC augmentation had numerically greater baseline OCD symptom severity (Y-BOCS mean 28.25 [$n = 4$] vs. 21.5 [$n = 14$]) as well as depression symptom severity (IDS-SR mean 49.2 [$n = 4$] vs. 38.4 [$n = 14$]) compared to those with a lesser response. Subjects with the more robust response also had significantly higher rumination severity at baseline measured by RRS (baseline RRS for stronger responders ($n = 4$) 72.5 vs. weaker responders ($n = 14$) 59.2, $P = 0.04$).

4. Discussion

These findings are consistent with our earlier report and indicate that treatment-resistant comorbid OCD MDD responds to multi-locus rTMS treatment at rates that compare favorably to medication or psychotherapy alone (Tadayonnejad et al., 2020). These results further suggest that those patients who do not show early improvement from DLPFC + SMA stimulation alone may benefit from right OFC augmentation stimulation. On average, the subjects who received OFC treatment had ~ 20% and ~37% improvement in OCD and depression symptom severity, respectively, with the most notable improvement in those with more severe baseline symptoms and greater rumination symptom severity.

This multi-locus targeting should be evaluated in the context of interconnected circuits involved in OCD-MDD symptoms genesis and therapeutic response. Dysfunction in cortico-striatal-thalamo-cortical (CSTC) circuits is strongly associated with OCD pathology (Dougherty et al., 2018; Goodman et al., 2021), while the evidence in depression implicates dysfunction in fronto-limbic networks (Tadayonnejad and Ajilore, 2014; Tadayonnejad et al., 2015). Application of rTMS to left DLPFC may alleviate depression symptoms in OCD-MDD by engaging pregenual anterior cingulate cortex and modulating function either *within* fronto-limbic circuits and/or *between* (CTSC- fronto-limbic) circuits (Tadayonnejad et al., 2018). We speculate that inhibitory rTMS to the SMA may dampen the habit circuit function (O'Doherty, 2016) and exert its therapeutic effect by alleviating the urge to perform habitual compulsions (Tadayonnejad et al., 2021). Our approach to targeting DLPFC and SMA is in line with findings of a recent meta-analysis of rTMS treatment studies in OCD in which high-frequency DLPFC and low-frequency SMA stimulation for OCD treatment were reported to be efficacious (Liang et al., 2021). While Liang et al. also reported that low-frequency OFC stimulation was not effective in patients with OCD, our study differs from the low-frequency OFC stimulation studies examined in that meta-analysis in two important respects. First, all of the OCD patients in our study had also severe treatment-resistant comorbid depression. Second, in our work, OFC site stimulation was used solely as an augmentation option rather than an independent treatment.

The involvement of a CTSC circuit incorporating OFC in OCD is supported by converging lines of evidence (Ahmari and Rauch, 2021; Price et al., 2021). Compared to healthy individuals, patients with OCD show hyperactivation in the OFC regions at baseline (Baxter et al., 1987). Furthermore, a reduction in OFC activity has been reported after SSRIs (Saxena et al., 1999), rTMS (Nauczyciel et al., 2014), and deep brain stimulation (Haynes and Mallet, 2010; Nuttin et al., 2003) treatment in individuals with OCD. These earlier findings are consistent with the results of the current study, in which inhibitory stimulation of right OFC was associated with reductions in both OCD (Nauczyciel et al., 2014; Williams et al., 2021) and depression (Feffer et al., 2018) symptoms. Our findings indicate that for some subjects not showing early improvement during DLPFC+SMA treatment for comorbid OCD and MDD, augmentation with inhibitory stimulation of the right OFC is safe and may improve outcomes of both OCD and MDD symptoms, particularly in affected individual with more intense OCD, depression, and rumination symptoms.

These results should be interpreted in the context of several limitations. First, all treatments were assigned using a measurement-based care paradigm in this study and, in the absence of randomized treatment assignment, it is not possible to draw cause-and-effect conclusions about changes in treatment and outcome. Second, the benefits of right OFC stimulation were most apparent in the most severely ill subjects. There were not a sufficient number of subjects and an imbalanced gender ratio in the present report to examine baseline symptoms' severity effects on treatment outcome. Third, the Y-BOCS assessment was not blind to the treatment condition and was not performed by an independent rater. Lastly, all subjects were receiving concomitant medication therapy for OCD and MDD, and it is possible that the outcomes were related to the combination of treatments rather than rTMS alone.

In conclusion, we propose a novel treatment approach in which sequential multi-locus rTMS applied to the DLPFC and SMA can be augmented by the addition of OFC stimulation in individuals not showing an early response to treatment. This protocol was safe, effective, and associated with symptom reduction in comorbid treatment-resistant OCD-MDD. Prospective controlled studies should examine the benefits of inhibitory OFC stimulation in OCD-MDD.

Author statement

RT, AFL contributed to the conception and design of the work. RT, TDPN, NDG, JGL, SAW, DK and AFL contributed to data collection. RTN, ACW, SAC, GC, CC and AFL contributed to the data analysis. RT, ACW, JC, AAB and AFL contributed to the interpretation of the results. RT, EH, JC and AFL wrote the main manuscript text. All authors reviewed the manuscript.

ACW has served as consultant to HeartCloud Inc. in the past 36 months. AFL has served as a consultant to NeoSync, Inc., Ionis Pharmaceuticals, Inc., iFovea, and ElMindA. He is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA), and has equity interest in BBA.

Acknowledgments

RT research is supported by the National Institute of Mental Health (K23MH116117, R01MH121089) and the Brain & Behavior Research Foundation (NARSAD-27111). We thank the Ryan Family for their generous support of innovative approaches to depression treatment and groundbreaking TMS technology.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114856.

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