Targeting Three Brain Regions (Bilateral SMA, Left and Right DLPFC) Sequentially in One Session Using Combined Repetitive Transcranial Magnetic Stimulation and Intermittent Theta-burst Stimulation in Treatment-refractory Obsessive-compulsive Disorder: A Case Report

Po-Han Chou¹², Alexander T. Sack³, Kuan-Pin Su⁴⁵⁶
¹Department of Psychiatry, China Medical University Hsinchu Hospital, China Medical University, Hsinchu, Taiwan; ²Department of Psychiatry, China Medical University Hospital, China Medical University, Taichung, Taiwan; ³Department of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands; ⁴College of Medicine, China Medical University, Taichung, Taiwan; ⁵Mind Body Interface Laboratory (MBI-Lab), China Medical University Hospital, Taichung, Taiwan; ⁶An-Nan Hospital, China Medical University, Tainan, Taiwan

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic disabling disorder with a lifetime prevalence of 2−3% [1], and 40−60% of patients remain refractory to first-line therapies [2]. In recent years, repetitive transcranial magnetic stimulation (rTMS) has been shown to be effective in treating refractory OCD [3]. The potential effective target sites and sequences include (1) both low frequency (LF) and high frequency (HF)-rTMS over the left or right dorsolateral prefrontal cortex (DLPFC); (2) LF-rTMS over the bilateral supplementary motor area (SMA); (3) HF-rTMS over the anterior cingulate cortex and medial prefrontal cortex (ACC/mPFC) and (4) intermittent theta burst stimulation (iTBS) over the left DLPFC (L-DLPFC) [4]. More recently, TMS using the so-called H-coil with HF-rTMS targeting the ACC/mPFC (BrainsWay Company, Jerusalem, Israel), as well as TMS using the so-called double-cone coil targeting bilateral DMPFC (Magventure, Farum, Denmark), have both been approved for the treatment of OCD by the US Food and Drug Administration [5,6]. The study reported that 38% of patients responded to deep TMS, whereas only 11% of patients responded to sham stimulation [6]. However, the deep TMS machine is not commonly available owing to its high cost, and the treatment response is still not satisfactory (i.e., 38% of patients showed > 30% reduction in Yale-Brown Obsessive Compulsive Scale [Y-BOCS]). To date, no previous studies have investigated the clinical results of combining effective protocols targeting different brain regions (i.e., SMA and bilateral DLPFC) in treatment-refractory OCD. Here, we report a patient with treatment-refractory OCD whose symptoms markedly improved with combined LF-R-DLPFC, LF-SMA, and iTBS-L-DLPFC treatment protocols.
**CASE**

An 18-year-old female student was referred to our department for first-episode treatment-refractory obsessive-compulsive disorder. In the last 12 months, she had developed intrusive and ego-dystonic obsessions, consisting mainly of pathological doubts regarding what her actions were disrespectful to God. She felt forced to spend a considerable amount of time engaged in mental rituals, consisting of repetitively apologizing and kneeling to the ground to relieve her fear and anxiety. Sometimes, she needed to kowtow to feel forgiven by God.

The patient had failed to respond to numerous antidepressant medications and combination therapies with atypical antipsychotics, including 60 mg paroxetine per day (4 weeks), 60 mg escitalopram per day (4 weeks), 60 mg fluoxetine per day (4 weeks), a combination of 200 mg sertraline and 400 mg sulpiride per day (4 weeks), and a combination of 90 mg duloxetine and 15 mg aripiprazole per day (5 weeks). When she first came to our clinic, she had been taking a combination of 225 mg venlafaxine, 300 mg bupropion, and 6 mg risperidone per day for more than 6 weeks, with a Y-BOCS score of 34 and 17-item Hamilton Rating Scale for Depression (HAMD-17) score of 18. Moreover, her quality of life was profoundly affected, as she suffered from frequent rituals of kowtow and an inability to attend school and engage in leisurely activities. Following the clinical interview, she was diagnosed with treatment-refractory OCD and major depressive disorder. After a comprehensive evaluation, she and her father provided written informed consent for rTMS therapy.

**rTMS Treatment Parameters**

Each treatment session consisted of rTMS over the R-DLPFC/SMA and iTBS over the L-DLPFC using a Magstim super-rapid stimulator (Magstim Company, Spring Gardens, UK) equipped with a vacuum-cooled 70-mm figure-of-eight coil. Stimulation parameters of LF-rTMS were 1 Hz, 20 minutes train (1,200 pulses/session) at 110% of resting motor threshold (RMT) sequentially applied to the right DLPFC [7] and the bilateral SMA [8]. Then, iTBS was applied with 20 trains of 10 bursts (short bursts of 3 stimuli at 50 Hz, repeated at 5 Hz) given at 8 seconds intervals, 600 pulses/session, 200 seconds at 80% RMT [4,9] targeting the L-DLPFC. For SMA rTMS, the coil was positioned over the SMA, localized via the 10–20 electroencephalogram (EEG) system, defined as 15% of the distance between the nasion and inion anterior to the vertex in the sagittal plane [10]. The coil was placed with the handle along the sagittal midline, pointing towards the occiput to stimulate bilaterally the SMA. For DLPFC rTMS, the coils were held by stands and tangentially placed over the patient’s DLPFC and rotated at a 45° angle from the midline. Coil localization was performed using an algorithm developed by Beam et al. [11]. Coils were placed over the Beam-F3 position when targeting the L-DLPFC with iTBS, and the Beam-F4 position when targeting the R-DLPFC with LF-rTMS. Stimulation of the three regions sequentially (i.e., R-DLPFC, SMA, and L-DLPFC) was performed one session per day, 5 days per week for 6 weeks, resulting in 30 sessions.

**Clinical Outcome**

After six weeks of therapy, the patient reported a remarkable improvement. There was a substantial reduction in the time occupied by OCD symptoms and distress, followed by increased control over obsessions and improved depressive symptoms (Table 1). The Y-BOCS score was 11 and HAMD-17 score was 8 after 6 weeks. No clinically significant side effects were observed.

**DISCUSSION**

To our knowledge, this is the first case report using combined rTMS/iTBS across three different brain target regions in each single session for the treatment of treatment-refractory OCD. Our case showed significant clinical improvement after 30 treatment sessions, without significant side effects. Previous studies have suggested that functional abnormalities of the cortico-striato-thalamocortical circuits and SMA might be central pathophysiological components of OCD [12]. The DLPFC, mPFC, orbitofrontal cortex (OFC), and ACC are also suggested to

| Symptoms | Baseline | 2nd week | 4th week | 6th week |
|-----------|----------|----------|----------|----------|
| YBOC-S    | 34       | 25       | 15       | 11       |
| HAMD-17   | 18       | 15       | 8        | 6        |

rTMS, repetitive transcranial stimulation; YBOC-S, Yale-Brown Obsessive-Compulsive Scale; HAMD-17, Hamilton Depression Rating Scale.
be functionally involved [12]. Previous rTMS studies in patients with OCD mainly focused on a single brain region with inconsistent target sites varying from the left DLPFC, right DLPFC, SMA, mPFC, and OFC. Interestingly, despite this range of potential targets, most of these studies demonstrated promising effectiveness in improving OCD symptoms when targeting any one of these brain regions [3]. In two recent meta-analyses, the authors concluded that LF-R-DLPFC, LF-SMA, and HF-L-DLPFC were likely to be more effective in treating OCD [3,13].

The rationale for targeting the bilateral SMA and right and left DLPFC with our protocols is related to the activation pattern of these regions in OCD. The SMA and R-DLPFC show extensive connections with regions implicated in motor control and response inhibition [14,15], with pathological hyperactivation in patients with OCD [12]. The 1 Hz stimulation applied over the SMA and R-DLPFC has an inhibitory effect and is thus expected to reduce activation in these regions [7,10]. Contrastingly, the L-DLPFC is involved in cognitive control [16] and increasing its activation is associated with improved control over intrusive thoughts in OCD [17]. Therefore, our protocol, aimed at increasing activity within the L-DLPFC using excitatory iTBS while decreasing activity in R-DLPFC and SMA using inhibitory LF-rTMS, is in line with the putative regions that are affected in OCD and involved in cognitive control and response inhibition/effects, respectively [12,18]. It also represents the exact three brain regions recommended recently as being effective for OCD in a meta-analysis. Considering the efforts and time investment when stimulating, not one, but three target sites within one session, we opted for iTBS instead of HF-rTMS (3 minutes duration vs. 38 minutes duration), which has recently been shown to be non-inferior to 10 Hz rTMS in the treatment of major depression [19]. This also considered the moderate level of depression in our patient.

The length and number of rTMS sessions can also affect the response rate, with a higher number of sessions providing more symptom reduction [20]. Our patient received 36000 R-DLPFC pulses, 36000 SMA pulses, and 18000 L-DLPFC pulses, thereby supporting this assumption because we observed a significant reduction in Y-BOCS scores even in treatment-refractory OCD with a relatively intensive treatment protocol. However, our case report should be interpreted with caution due to the lack of a placebo control. Moreover, our case was at an early stage of her illness, and the effect of our rTMS protocol in patients with chronic refractory OCD needs to be confirmed. Our case report also highlights the importance of personalized treatment plans according to psychiatric comorbidities in patients with OCD [21].

In conclusion, our case report demonstrates the feasibility and effectiveness of targeting three different brain regions within one session of TMS OCD therapy using a combination of rTMS/iTBS treatment to the bilateral DLPFC and SMA in treatment-refractory OCD. Future studies with larger sample sizes and randomized, double-blind, and placebo-controlled trials are warranted to confirm our findings.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Po-Han Chou. Data acquisition: Po-Han Chou. Supervision: Kuan-Pin Su and Alexander T. Sack. Writing—original draft: Po-Han Chou. Writing—review & editing: Kuan-Pin Su and Alexander T. Sack.

ORCID

Po-Han Chou https://orcid.org/0000-0002-4148-457X
Alexander T. Sack https://orcid.org/0000-0002-1471-0885
Kuan-Pin Su https://orcid.org/0000-0002-4501-2502

REFERENCES

1. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry 2010;15:53-63.
2. Simpson HB, Huppert JD, Petkova E, Foa EB, Liebowitz MR. Response versus remission in obsessive-compulsive disorder. J Clin Psychiatry 2006;67:269-276.
3. Liang K, Li H, Bu X, Li X, Cao L, Liu J, et al. Efficacy and tolerability of repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. Transl Psychiatry 2021;11:332.
4. Naro A, Billeri L, Cannavò A, De Luca R, Portaro S, Bramanti P, et al. Theta burst stimulation for the treatment of obsessive-compulsive disorder: a pilot study. J Neural Transm (Vienna) 2019;126:1667-1677.
5. Roth Y, Tendler A, Arikan MK, Vidrine R, Kent D, Muir O, et al. Real-world efficacy of deep TMS for obsessive-compulsive disorder: post-marketing data collected from twenty-two clinical sites. J Psychiatr Res 2021;137:667-672.

6. Carmi L, Tendler A, Bystritsky A, Hollander E, Blumberger DM, Daskalakis J, et al. Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. Am J Psychiatry 2019;176:931-938.

7. Seo HJ, Jung YE, Lim HK, Um YH, Lee CU, Chae JH. Adjunctive low-frequency repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex in patients with treatment-resistant obsessive-compulsive disorder: a randomized controlled trial. Clin Psychopharmacol Neurosci 2016;14:153-160.

8. Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. Int J Neuropsychopharmacol 2010;13:217-227.

9. Chou PH, Lu MK, Tsai CH, Hsieh WT, Lai HC, Shiyakov S, et al. Antidepressant efficacy and immune effects of bilateral theta burst stimulation monotherapy in major depression: a randomized, double-blind, sham-controlled study. Brain Behav Immun 2020;88:144-150.

10. Mantovani A, Lisanby SH, Pieraccini F, Ullivelli M, Castrogiovanni P, Rossi S. Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette’s syndrome (TS). Int J Neuropsychopharmacol 2006;9:95-100.

11. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul 2009;2:50-54.

12. Stein DJ, Costa DCL, Lochner C, Miguel EC, Reddy YCJ, Shavitt RG, et al. Obsessive-compulsive disorder. Nat Rev Dis Primers 2019;5:32.

13. Rehn S, Eslick GD, Brakoulias V. A meta-analysis of the effectiveness of different cortical targets used in repetitive transcranial magnetic stimulation (rTMS) for the treatment of obsessive-compulsive disorder (OCD). Psychiatr Q 2018:69:65-665.

14. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 2004;8:170-177.

15. Picard N, Strick PL. Imaging the premotor areas. Curr Opin Neurobiol 2001;11:663-672.

16. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167-202.

17. Zhou DD, Wang W, Wang GM, Li DQ, Kuang L. An updated meta-analysis: short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorders. J Affect Disord 2017;215:187-196.

18. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 2008;32:525-549.

19. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feifer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 2018;391:1683-1692.

20. Haghighi M, Shayganfard M, Jahangard L, Ahmadpanah M, Bajoghi H, Pirdkehghan A, et al. Repetitive Transcranial Magnetic Stimulation (rTMS) improves symptoms and reduces clinical illness in patients suffering from OCD—results from a single-blind, randomized clinical trial with sham cross-over condition. J Psychiatr Res 2015:68:238-244.

21. Chou PH, Lin YF, Lu MK, Chang HA, Chu CS, Chang WH, et al. Personalization of repetitive transcranial magnetic stimulation for the treatment of major depressive disorder according to the existing psychiatric comorbidity. Clin Psychopharmacol Neurosci 2021;19:190-205.