

Clinical Psychopharmacology and Neuroscience – Manuscript Submission

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- **Title:** 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
- **Running Title:** rTMS in refractory OCD
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- **KeyWords:** obsessive compulsive disorder, OCD, repetitive transcranial stimulation, rTMS, theta burst stimulation, TBS

Abstract

Repetitive transcranial magnetic stimulation (rTMS) has been widely used as a therapy for refractory obsessive-compulsive disorder (OCD). However, it remains unclear which exact target and stimulation sequence of rTMS is most effective for OCD. Here, we report the case of an 18-year-old woman with treatment-refractory OCD whose symptoms markedly improved after combined rTMS and intermittent theta-burst stimulation over the bilateral dorsolateral prefrontal cortex and supplementary motor area. Our report indicates that combining treatment sequences that stimulate different brain regions sequentially is feasible and may clinically benefit patients suffering from OCD.

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) (3); 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), as well as TMS using the so-called double-cone coil targeting bilateral DMPFC (MagVenture), 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 report

Miss H, 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 Miss H 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 (HAM-D-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 leisureable 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 Ltd, UK) equipped with a vacuum-cooled 70-mm figure-of-eight coil. Stimulation parameters of LF-rTMS were 1 Hz, 20 min train (1200 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 s intervals, 600 pulses/session, 200 s at 80% RMT [4, 9] targeting the L-DLPFC. For SMA rTMS, the coil was positioned over the SMA, localized via the 10 – 20 EEG system, defined as 15% of the distance between the nasion andinion 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-thalamo-cortical circuits and SMA might be central pathophysiological components of OCD [12]. The DLPFC, mPFC, orbitofrontal cortex (OFC), and ACC are also suggested to 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 DLPOFC, 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 min duration vs. 38 min 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, Miss H 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.

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Table 1. Clinical outcomes during the rTMS treatment of Miss H.

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

YBOC-S, Yale-Brown Obsessive-Compulsive Scale; HAMD-17, Hamilton Depression Rating Scale

CONSENT FORM FOR CASE REPORTS¹

Name of person described in article or shown in photograph: Miss H

Medical practitioner or corresponding author: Po-Han Chou, MD.

I Hu, Ya-Ting give my consent for this information about Hu, Ya-Ting, relating to the subject matter above ("the Information") to appear in a journal article, or to be used for the purpose of a thesis or presentation.

I understand the following:

1. The Information will be published without my name/child's name/relatives name attached and every attempt will be made to ensure anonymity. I understand, however, that complete anonymity cannot be guaranteed. It is possible that somebody somewhere - perhaps, for example, somebody who looked after me/my child/relative, if I was in hospital, or a relative - may identify me.
2. The Information may be published in a journal which is read worldwide or an online journal. Journals are aimed mainly at health care professionals but may be seen by many non-doctors, including journalists.
3. The Information may be placed on a website.
4. I can withdraw my consent at any time before online publication, but once the Information has been committed to publication it will not be possible to withdraw the consent.

Signed: Hu Ya-Ting Date: 2021.11.22

Signature of requesting medical practitioner/health care worker:

Chengyuan Date: 2021.11.22

¹ Adapted from *BMJ Case Reports* consent form.