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Sequential multi-locus transcranial magnetic stimulation for treatment of obsessive-compulsive disorder with comorbid major depression: A case series

Obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) are highly comorbid [1], with depressive symptoms amplifying the chronicity and severity of OCD symptoms. Comorbid illness decreases quality of life and daily functioning [2] and is associated with greater suicidality and more frequent inpatient hospitalizations [3]. Furthermore, comorbid OCD/depression is associated with poorer response to OCD-focused psychological and pharmacological treatments [4]. Epidemiologic studies have shown that OCD symptoms generally precedes the occurrence of depression, suggesting a causal interacting model in which OCD predisposes to development of depressive symptoms [5]. In line with that causal model, Tadayonnejad et al. showed aberrant effective (directional) connectivity between OCD and MDD circuits may be a potential network mechanism of depressive symptom genesis or worsening in OCD-MDD [6]. The challenging nature of this comorbidity necessitates the development of novel, more effective treatments.

In this study, we tested an innovative multi-site repetitive transcranial magnetic stimulation (rTMS) protocol to target OCD and MDD circuits in seven patients with refractory comorbid OCD-MDD (5 males, 2 females, mean age 35 ± 7.92, 6/7 on medications). Consent for treatment was obtained from all patients. The UCLA Institutional Review Board approved this retrospective analysis of de-identified data. Patients had high baseline OCD (mean Yale–Brown Obsessive Compulsive scale [Y-BOCS] score of 24.2 ± 3.15) and depressive symptoms (mean Inventory of Depressive Symptomatology-Self-Report [IDS-SR] score of 45.1 ± 13.48). Before seeking TMS treatment, each patient had tried 4–14 different psychotropic medications (average 6.8 ± 3.7 medications including SSRIs and antipsychotics) and 2–3 courses of psychotherapy (average 2.4 ± 0.5 including cognitive behavior therapy and/or exposure and response prevention), resulting in a non-optimal improvement. The average duration of OCD and MDD conditions across patients was 22 ± 5.8 years and 16 ± 4.6 years, respectively.

Patients received 36 rTMS sessions. Each session included 10 Hz excitatory rTMS (3000 pulses) or intermittent theta burst stimulation (iTBS; 600 pulses) over the left dorsolateral prefrontal cortex (DLPFC) followed by 1200 pulses of 1Hz inhibitory rTMS over the bilateral supplementary motor area (SMA). Motor threshold (MT) for each patient was determined during session 1 and treatment intensity was titrated to 120% MT for the left DLPFC and 130% for the SMA as tolerated. Patients showed a robust therapeutic response in both OCD (Y-BOCS on T36:12.71 ± 5.56; $P = 0.0013$) and depressive (IDS-SR on T36: 19.29 ± 7.13; $P = 0.0017$) symptoms. Five out of seven patients showed full OCD response (≥35% reduction in Y-BOCS) and five patients showed full depression response (≥50% reduction in IDS-SR scores). The two remaining patients showed partial response of both OCD and MDD symptoms (20–34% reduction in Y-BOCS, 30–50% reduction in IDS-SR scores) (Fig. 1). There were no adverse events leading to treatment discontinuation. All patients were treated during the past 1.5 years and none has returned for retreatment, although systematic post-treatment follow-up data are not available.

Therapeutic mechanisms of the DLPFC and SMA stimulation may be understood in the context of interconnected circuits of which those regions are important components. DLPFC is a part of the Default Mode Network (DMN), which has been reported to have aberrant function in both OCD and MDD [7,8]. The therapeutic benefit of DLPFC stimulation may be mediated through connections to the subgenual [9] and pregenual [10] anterior cingulate cortex. Interestingly, in Tadayonnejad et al. (2018) study, pregenual anterior cingulate cortex was shown to mediate the abnormal interaction between cortico-striatal-thalamo-cortical OCD and fronto-limbic MDD circuits. We suggest that DLPFC TMS by modulating pregenual anterior cingulate cortex function not only impacts *within* (DMN) circuit dynamics but also *between* (OCD and MDD) circuits interaction. Furthermore, we speculate that inhibitory rTMS to the SMA by dampening the habit circuit (SMA-putamen) provides its therapeutic effect by alleviating the urge to perform habitual compulsions.

In comorbid psychiatric conditions like OCD-MDD, aberrant dynamics exist not only within but also between multiple interconnected circuits. We suggest that targeting multiple brain regions through an approach such as that described here is a good therapeutic strategy to normalize pathological dynamics within and between the involved circuits in OCD-MDD and other comorbid psychiatric conditions. These preliminary results in this group of highly treatment-resistant OCD-MDD patients are encouraging and need to be replicated in prospective sham-controlled studies with larger sample sizes.

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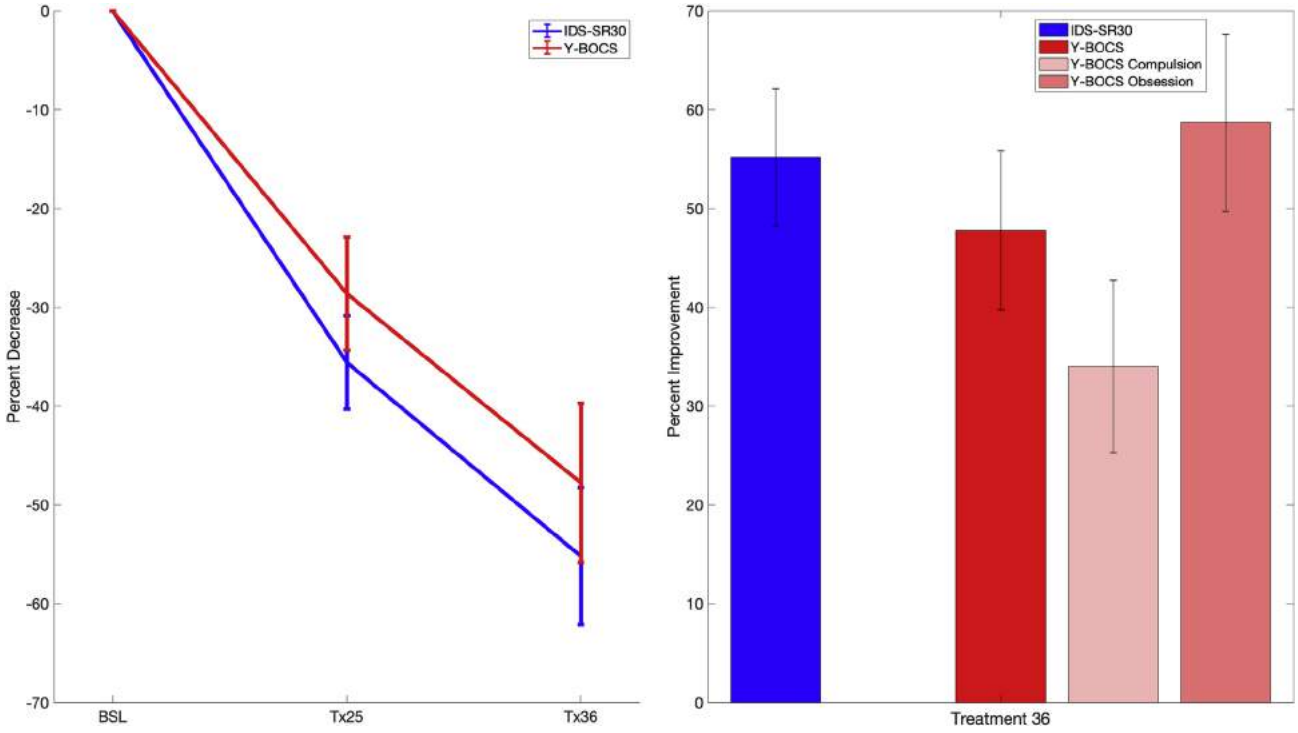

Fig. 1. Graphs of depression (Blue) and OCD (Red) symptom severity decrease over the course of 36 sequential multi-locus TMS treatment sessions in 7 patients with refractory comorbid OCD and in response to the left DLPFC (excitatory) and SMA (inhibitory) TMS (*right*); graph bars of average depression, total OCD and obsession and compulsion subcomponents of OCD symptom severity percent reduction (left). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Declaration of competing interest

The authors declare no conflict of interest. Mr. Wilson has served as a consultant to HeartCloud, Inc. Dr. Leuchter has received research support from the CHDI Foundation, the Department of Defense, Neuronetics, NeuroSigma, and NIH; he has served as a consultant to ElMindA, Ionis Pharmaceuticals, and NeoSync; and, he is chief scientific officer of and has equity interest in Brain Biomarker Analytics. The rest of authors report no financial relationships with commercial interests.

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