

Case Report

Multiple Target Repetitive Transcranial Magnetic Stimulation (rTMS) Combined with Neurofeedback for Complete Resolution of Severe OCD, Bipolar Depression, and Anxiety

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Obsessive compulsive disorder (OCD) is a prevalent disabling condition and often comorbid with depression, anxiety, and high suicide rates. First line treatments of OCD such as Selective Serotonin Reuptake Inhibitors (SSRIs) and dopamine antagonists, and mood stabilizers fail to treat OCD in up to 60% of patients [1]. Transcranial magnetic stimulation has emerged as a non-pharmacological alternative for treatment of OCD and several case reports and randomized trials have shown positive response although the efficacy of rTMS remains low at approximately 35% with little positive effects on reversing comorbidities including symptoms of depression and anxiety [2]. The most effective stimulation parameters, cortical targets, and type of coil (figure of eight, H-coil, cone, or deep) for rTMS have not been established. Investigators report positive outcomes with stimulation of the right Orbitofrontal Cortex (OFC), Supplementary Motor Area (SMA), and Anterior Cingulate Cortex (ACC) [2,3]. Recently, deep rTMS directed at ACC has shown significant benefit [4]. In addition, neurofeedback, also known as 'EEG biofeedback', has been established as an effective treatment of various psychological and neuropsychiatric disorders including OCD, anxiety, and depression [5,6]. Accordingly, I hypothesize that a more formidable outcome can be achieved in patients suffering from OCD accompanied by comorbidities when: 1) multiple cortical targets are stimulated under one treatment regimen; 2) multiple stimulation parameters are utilized in response to patient report of outcome; and 3) neurofeedback is used in conjunction with rTMS. This 'combination approach' was in fact, found to be significantly effective in treatment of pervasive spectrum disorder, e.g. autism and early signs of dementia [7,8]. Here, I present the first case report of patient with severe OCD, anxiety, and depression who showed marked improvement and resolution of OCD, anxiety, and depression following completing total of 41 sessions of rTMS and 15 sessions of 'Z-score neurofeedback'.

Patient is 33-year-old male diagnosed with over 15 years of OCD, generalized anxiety, and bipolar depression. Patient has undergone trials of Serotonin Reuptake Inhibitors (SSRIs), mood stabilizers including lithium and valproic acid, and benzodiazepines including lorazepam. At time of presentation to my clinic, patient's

primary symptoms included obsessive thoughts with facial and skin contamination, recurrent feeling of self-guilt, marked difficulty with anxiety in dark environments, agoraphobia, poor self-worth, and extreme spells of depression, manic, and hypomanic episodes. In addition, patient displayed severe hypochondriasis with respect to various disorders including motor neuron disease, multiple sclerosis, and infections. Moreover, patient experienced various somatic symptoms including non-specific vibratory sensations of mouth, trunk, and extremities. At onset, Yale Brown Obsessive Compulsive Score (Y-BOCS) was 19, Burn's anxiety score was 36, Burn's depression score was 22, and PHQ-9 of 10. Risks and benefits of rTMS including off-label use of rTMS parameters were discussed in detail with patient and written signed consent obtained. A brain MRI was obtained to include skin fiducial markers for navigation software (*The Neural Navigator*, Brain Science Tools, Utrecht, Netherlands) 1mm sagittal and axial T1 MRI images were processed and segmented to identify several cortical targets including: left and right Dorsolateral Prefrontal Cortex (DLPFC), right OFC, left Dorsomedial Prefrontal Cortex (DMPFC), and ACC. On initial visit and every 5-6 visits, the Motor Threshold (MT) was determined as the intensity required to activate the left Abductor Pollicis Brevis (APB) and/or the First Dorsal Interosseus (FDI) on the contralateral hand on average of 5 of 10 single pulse trials directed at left motor cortex per visual inspection. Patient was interviewed and underwent daily rTMS sessions using varying targets and stimulation parameters (see table). The rTMS stimulation parameters were chosen based on current trial evidence for treatment of OCD, depression, and anxiety and patient's daily report of signs and symptoms. All stimulations were performed using figure-of-eight coil (Neurosoft, Ltd. Ivanovo, Russian Federation) rTMS machine. Cortical targets included SMA, left DLPFC, right DLPFC, left DMPFC, ACC, and right OFC. Cortical targets were identified and marked using navigation software.

Neurofeedback was done using *Neuroguide 'Z-Score LORETA'* neurofeedback software by collecting and editing 4 minutes of baseline EEG and creating a 'symptoms checklist match' (for detail of procedure see Thatcher & Lubar, Z Score Neurofeedback: Clinical

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Treatment Date	Location of Stimulation	Frequency (Hz)	Inter-train interval (sec)	Treatment Intensity (% of MT)	Pulses in Train	No. of Trains	MT	Total Pulses
1	7/9/2018 SMA	1 Hz	60	100%	300	4	57	1200
2	7/10/2018 SMA	1 Hz	60	100%	300	4	57	1200
3	7/11/2018 SMA	1 Hz	60	100%	300	4	57	1200
4	7/12/2018 SMA	1 Hz	60	100%	300	4	57	1200
5	7/13/2018 SMA	1 Hz	60	100%	300	4	57	1200
6	7/16/2018 LDLPFC	iTBS	10	80%	30	60	60	1800
7	7/17/2018 LDLPFC	iTBS	10	80%	30	60	60	1800
8	7/18/2018 LDLPFC	iTBS	10	80%	30	60	60	1800
9	7/19/2018 LDLPFC	iTBS	10	80%	30	60	60	1800
10	7/20/2018 LDLPFC/RDLPFC	iTBS/cTBS	10--1	80--80%	30/300	60--6	60/65	1800/1800
11	7/23/2018 RDLPFC	1 Hz	1	80%	20	45	60	900
12	7/24/2018 RDLPFC	1 Hz	1	80%	20	45	60	900
13	7/25/2018 RDLPFC	1 Hz	1	80%	20	45	60	900
14	7/26/2018 LDLPFC/RDLPFC	iTBS/cTBS	10--1	80--80%	30/300	60--6	60/60	1800/1800
15	7/27/2018 LDLPFC/SMA	iTBS/1 Hz	10--60	80--100%	30/300	60--4	60/60	1800/1200
16	7/30/2018 LDLPFC/SMA	iTBS/1 Hz	10--60	80--100%	30/300	60--4	60/60	1800/1200
17	7/31/2018 LDLPFC/SMA	iTBS/1 Hz	10--60	80--100%	30/300	60--4	60/60	1800/1200
18	8/1/2018 LDLPFC/SMA	iTBS/1 Hz	10--60	80--100%	30/300	60--4	60/60	1800/1200
19	8/2/2018 LDLPFC/SMA	iTBS/1 Hz	10--60	80--100%	30/300	60--4	60/60	1800/1200
20	8/3/2018 RDLPFC	cTBS	0	80%	1800	1	60	1800
21	8/9/2018 LDLPFC/SMA	iTBS/1 Hz	10--60	80/100%	30/300	60--4	60/60	1800/1200
22	8/10/2018 LDLPFC/SMA	iTBS/1 Hz	10--60	80/100%	30/300	60--4	60/60	1800/1200
23	8/13/2018 LDLPFC/SMA	iTBS/1 Hz	10--60	80/100%	30/300	60--4	60/60	1800/1200
24	9/10/2018 LDLPFC/RDLPFC/ACC/OFC	10/10/10/1	26/26/26/0	120/120/140/100%	40/40/40/300	41/41/25/4	55/57	1640/1640/1000/1200
25	9/11/2018 LDLPFC/RDLPFC/ACC/OFC	10/10/10/1	26/26/26/0	120/120/140/100%	40/40/40/300	41/41/25/4	55/57	1640/1640/1000/1200
26	9/12/2018 RDLPFC	10	26	120%	40	125	57	5000
27	9/13/2018 RDLPFC	10	26	120%	40	125	57	5000
28	9/14/2018 RDLPFC	10	26	130%	40	125	57	5000
29	9/17/2018 LDLPFC/RDLPFC/ACC/OFC	10/10/10/1	26/26/26/0	120/120/130/130%	40/40/40/300	41/41/25/4	55/57	1640/1640/1000/1200
30	9/19/2018 LDLPFC/RDLPFC/ACC/OFC	10/10/10/1	26/26/26/0	110/120/140/120%	40/40/40/300	41/41/25/4	55/57	1640/1640/1000/1200
31	9/20/2018 LDLPFC/RDLPFC/ACC/OFC	10/10/10/1	26/26/26/0	120/110/140/120%	40/40/40/300	41/41/25/4	55/57	1640/1640/1000/1200
32	9/21/2018 LDLPFC/RDLPFC/ACC/OFC	10/10/10/1	26/26/26/0	120/110/140/120%	40/40/40/300	41/41/25/4	55/57	1640/1640/1000/1200
33	9/24/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600
34	9/25/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600
35	9/26/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600
36	9/27/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600
37	10/2/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600
38	10/3/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600
39	10/4/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600
40	10/5/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600
41	10/8/2018 LDLPFC/RDLPFC/ACC/OFC/LDMPFC	10/10/10/1/iTBS	26/26/26/0/10	120/120/140/120/100%	40/40/40/300/30	41/41/25/4/20	55/57	1640/1640/1000/1200/600

Legend	SMA	supplementary motor area
	LDLPFC	left dorsolateral prefrontal cortex
	RDLPFC	right dorsolateral prefrontal cortex
	ACC	anterior cingulate cortex
	OFC	right orbital frontal cortex
	LDMPFC	left dorsomedial prefrontal cortex
	iTBS	intermittent theta burst
	cTBS	continuous theta burst

Applications, 2015; Thatcher, Latest Developments in Live Z-Score Training: Symptom Check List, Phase Reset, and Loreta Z-Score Biofeedback, 2013) [9,10]. Each session consistent of five 5-minute rounds for total of approximately 25-30 minutes. Dry, wireless, headset (DSI-24, Wearable Sensing, San Diego, CA, USA) was used to gather EEG recordings and conduct neurofeedback sessions. Patient underwent neurofeedback approximately two times per week, usually prior to or after r TMS sessions. Patient showed progressive and marked improvement in, OCD, anxiety, and depression. Y-BOCS scores showed 63% improvement (19 to 7), Burn's depression showed 86% improvement (22 to 3), Burn's anxiety showed 72% improvement (36 to 10), and PHQ-9 showed 70% improvement (from 10 to 3). Patient reported complete reversal of agoraphobia, self-contamination delusions, and depression. He reported feeling quite comfortable with going to large dark movie theater, avoiding washing rituals, denied panic attacks in provocative environments (e.g. driving), and developed markedly improved mood. The clinical improvements were noticeable by father and other close relatives. Although we delivered higher intensity of stimulation and overall larger total daily pulses, patient reported no significant adverse effects and did not experience seizures. To our knowledge, this is first report of 1) applying rTMS to multiple (e.g. more than 2) cortical targets on one patient with each utilizing separate stimulation protocols, and 2) adding neurofeedback to treatment regimen leading to marked improvement and resolution of OCD together with anxiety and depression.

The rationale behind use of various cortical targets is to modulate several circuits that may be contributing to OCD and comorbidities including abnormal connectivity and/or neuronal hyperactivity within cortical-striate-thalamic-cortical circuits--currently the leading working model regarding the pathophysiology of OCD [4]. One randomized, sham-controlled study showed modest improvements in OCD (29% reduction on Y-BOCS) and depression (48% on HAM-D) symptoms after 14 sequential 1 Hz stimulation sessions targeting left DLPFC and SMA [11,12]. Additional randomized sham-controlled studies applying a multi-target approach and in combination with neurofeedback will be helpful and can potentially significantly increase the efficacy rate of treatment.

Keywords: Generalized anxiety disorder, Multiple targets rTMS, Neurofeedback, Obsessive compulsive disorder, Repetitive transcranial magnetic stimulation

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