ORIGINAL ARTICLE

The Efficacy of Combined Transcranial Magnetic Stimulation and Exposure Prevention Response on Symptoms of Resistant Obsessive Compulsive Disorder: An Intensive Day Care Program

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Received: 08 September 2022 / Accepted: 13 November 2022

Abstract

Purpose: Obsessive-Compulsive Disorder (OCD) is a mental and behavioral disorder in which an individual has intrusive thoughts and rituals which decrease the distress. It seems that there are many treatments such as EX/RP, repetitive Transcranial Magnetic Stimulation (rTMS), medications or mindfulness for OCD, but there is no single effective treatment yet. In this study, we investigated a multi-element daily program on symptom reduction of OCD people.

Materials and Methods: In a quasi-experimental design 13 patients were included in the study and received daily rTMS with EX/RP and biofeedback. We utilized BDI, BAI, and YBOCS tools to collect data before and after the treatment and in the subsequent one-month follow-up.

Results: According to the BDI, BAI, and YBOCS results, the decrease in score was observed at the $p<0.001$ level and the changes were significant after a one-month follow-up period.

Conclusion: The results indicated that the combination of sequenced treatments simultaneously such as rTMS and biofeedback with exposure therapy can facilitate the engagement and enhancement of self-control and distress tolerance.

Keywords: Obsessive-Compulsive Disorder; Exposure Prevention Response; Repetitive Transcranial Magnetic Stimulation; Biofeedback.

DOI: https://doi.org/10.18502/fbt.v11i1.14509

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1. Introduction

Unwanted, repetitive, thoughts, images, or impulses (obsessions) and time-wasting behaviors (compulsions) with 2-3% lifetime prevalence are the main characteristics of Obsessive-Compulsive Disorder (OCD) [1].

The currently approved treatments of OCD are Exposure Response Prevention (ERP) therapy [2], selective serotonin reuptake inhibitors [3], repetitive Transcranial Magnetic Stimulation (rTMS) [4], and intensive residential program [5]. However, despite utilizing all these modules about a third to half of the patients fail to respond to treatment [6]. Nevertheless adding SSRIs to psychological methods seems to have the most effective therapeutic outcomes [7].

Notwithstanding the supporting research on the efficacy of exposure therapy as the first-line treatment of OCD, there exist some negative beliefs about this method in patients and therapists alike. The main reason is the increase in distress and high levels of anxiety during exposure therapy which may lead to dropout or refusal in patients [8]. Due to this anxiety-provoking nature of ERP, other CBT methods such as mindfulness-based interventions—which force the patient to observe their thoughts and refrain from compulsively acting on them [9]—play a more effective role in the management of distress due to obsessive-compulsive disorder treatment [10].

Based on current knowledge the accurate pathophysiology of OCD is not completely clear, but it is supposed that OCD is associated with dysfunctional networks which are due to the orbitofronto-striato-pallido-thalamic circuitry [11, 12]. These circuits are most included:

1- The Dorsolateral Prefrontal Cortex (DLPFC), which is linked to deficits in monitoring, working memory, and higher-level planning in OCD [13].

2- Anterior cingulate gyrus and supplementary motor (SMA) which may explain deficient inhibitory control over behavior in patients with OCD [14].

3- Hyperactivity of the orbitofrontal cortex (OFC) (Chamberlain, 2008) can be associated with information processing and response control dysregulation [15, 16].

4- Thalamus which acts as a relay station between the striatum and cortex, playing a key role in perception and thoughts integration, motor function, sensory information used in motor control between the basal ganglia, the cerebellum, and cortical motor areas in OCD people [17].

In addition to the aforementioned traditional psychological and pharmacological treatments, novel and efficient neuromodulation techniques such as rTMS can be utilized to target the various parts of this circuitry more focally and effectively [18]. For this purpose, deep rTMS, which has been approved for OCD in 2016 can affect Cortico-Striato-Thalamo-Cortical circuits (CSTC) [19]. However, standard rTMS with altering the excitability of different brain regions such as the Supplementary Motor Area (SMA) can still decrease obsessions and high levels of distress by regulating information processing and response control [20]. Hyperactivity in the SMA may indicate the role of inhibitory control deficiency on compulsive behaviors in patients with OCD [21], as it has an association with striat-thalamus regions involved in response control [22]. Also, the research indicated that changing sensory experience by mindfulness methods, which can be associated with some areas like the thalamus can have impressive effects on response control and subsequently relapse management [23].

Hence, the combination of sequenced neuromodulation treatments such as rTMS and biofeedback with exposure therapy can facilitate the engagement and enhancement of self-control and toleration of the distress caused by response prevention.

In this paper, we hypothesized the effect of inhibitory rTMS on SMA and illustrate it can decrease response inhibition and processing error. Therefore, utilizing rTMS in this region can be considered an effective method for patients to tolerate and control their rituals during EX/RP. Therefore, we conceptualized it with an intensive, multi-element daycare program with a combination of 20 rTMS sessions (six times a week) with ERP sessions, and an HRV biofeedback as a mindfulness treatment to control their thoughts and rituals twice per week as a relapse management module. We will finally conclude whether this combinatory method tends to be highly efficacious and can significantly enhance compliance with exposure response prevention.

2. Materials and Methods

2.1. Subjects

In a one-time series quasi-experimental design, 13 patients (10 females and 3 males) between 20 to 50 years of age who were referred to Atieh Clinic after diagnosing with OCD by a psychiatrist according to the fifth version of DSM5 after completion of a consent form were included in the study. The exclusion criteria were the existence of head trauma or seizure history in the individuals or their family, a history of bipolar disorder, psychotic symptoms, substance abuse, pregnancy, or having metal, any prosthesis or shunt in the skull or peacemaker. The factor of medication resistance was also considered according to the definition that the patient had not shown a therapeutic response to at least two different anti-obsessive agents with sufficient dose and duration of use.

2.2. Experimental Procedure

We utilized BDI, BAI, and YBOCS tools to collect data before and after the treatment and in the subsequent one-month follow-up. In our study, each subject was admitted to the Atieh department day care center from Saturday to Thursday from 9:00 AM to 12:00 AM. The TMS therapist exposed the patients to the toilet and wanted them to touch the floor, wall, and toilet handle. In addition, for ERP protocol [24], we asked the patient to take off his shoes or put their wet hands on the ground in the severe stages of exposure. After the EX, people received the first TMS session without any prevention response. At the end of the first rTMS session, the patient was given a rest while no washing was allowed. At this time, patients had to drink water to feel the need to go to the toilet. After half an hour they should repeat the exposure with floor, handle and wall, and toilet trash again and wash the floor with a dirty brush, and sited under the TMS coil. During the treatment, the clients were not permitted to have any distractions, relaxation, or reassurance. In the end, a biofeedback session was performed for the patient, and the abdominal breathing exercise was taught with a 4-second, 6-second exhalation protocol to increase their mindfulness. In the biofeedback session, the patient had to mentally recall their fears and perform abdominal breathing at the same time. As the home exercise, the patients were also asked to do five-minute mental imagery about exposing to contamination and abdominal breathing three times a day at scheduled times. It is worth mentioning that during the TMS session, the therapist did not reassure the patient and encouraged them to tolerate their distress level or even make it worse.

2.3. rTMS

rTMS was performed with a Neuro MS rTMS device by a figure-of-8-shaped coil. Active Motor Threshold (AMT) was selected which has been defined as the minimum stimulus intensity to produce a motor-evoked response in Abductor Policies Brevis muscle (APB). Protocol of TMS was delivered at 120% of AMT. The frequency was 1 Hz for 30 min, 1800 pulses per session (36,000 pulses over twenty sessions). The site of stimulation (supplementary motor) is on Fcz by 10-20 international system.

2.4. Statistical Analysis

YBOCS, BDI, and BAI depression tests were completed immediately after 20 sessions and 4 weeks later. Repeated measures analysis of variance (RANOVA) was used to analyze the data.

3. Results

Two subjects were excluded from the initial study design (due to non-cooperation with treatment and headache) and a total of 13 subjects were included in this study. The mean age of the group was 35 years (± 8y). Because the inclusion was based on patients who presented to the clinic for treatment with the drug resistance and rTMS inclusion criteria, more women than men were included. The demographics of this group are described in Table 1.

The results of YBOCS have been shown in Table 2. As findings, the treatment reduced YBOCS total scores from 31.00 ± 3sdt to 13 ±2.00 sdt at the end of the follow-up, which is due to points decrease. Through rANOVA, there was seen a significance at $p<0.0001$ level ($F=65/09$, $\eta 2= 0.79$) (Table 2). To get to the point where these changes take place, the average of this scale was compared with paired-sample t-test. The results are shown in Table 3.

Table 1. Demographic charachteristics of subjects

Patients	Medications	Age	Gender	Length of illness (year)
1	Clomipramine/fluoxetine	37.00	Female	12
2	flouxetine /haloperidol	47.00	Female	2
3	Asentra/trifluprazine	41.00	Male	7
4	Haloperidol/clomipramine	29.00	Male	3
5	Fluoxetine	28.00	Female	10
6	Fluoxetine	33.00	Female	12
7	Clomipramine	21.00	Female	11
8	flouxetine /haloperidol	40.00	Female	3
9	Fluoxetine	51.00	Female	5
10	flouxetine /haloperidol	29.00	Female	9
11	Fluoxetine	28.00	Female	4
12	flouxetine /haloperidol	36.00	Female	2
13	Haloperidol/clomipramine	35	Male	7

Table 2. YBOCS results: changes in severity of symptoms based on Yale Brown obsessive compulsive Scale

All patients	Pre	Post	One-month follow-up
Mean	31.08	14.0	13.0
Standard Deviation	3.0	2.07	2.0
η2	0.79		
F	0.65		
Significance	P<0.0001		

Table 3. Paired Samples t-Test in YBOCS scores

		Mean	Std. Deviation	t	sig
Pair 1	YBOCSpre	31.0	3.0	5.0	0.000
	YBOCS1week	23.0	4.0		
Pair 2	YBOCS1week	23.0	4.0	3.0	0.003
	YBOCS10th	20.0	3.0		
Pair 3	YBOCS10th	20.0	3.0	4.0	0.01
	YBOCS20th	14.0	2.0		
Pair 4	YBOCS20th	14.0	2.0	1.0	0.000
	YBOCSfollow	13.0	2.0		

There's a significant reduction in the t-test between the first session to 1 week after (p<0.0001), the first week to the 10th session to (p<0.003), and the 10th session to the 20th session of treatment (p<0.001).

According to results, there was a significant reduction decrease of the score of BDI (p<0.001 level (F= 29.0, η2, p<0/0001) (Table 4). Also, there's a significant reduction in the t-test between the first session to 1 week after (p<0.0001), the first week to the 10th session to (p<0.04), and the 10th session to the 20th session of treatment (p<0.0001) (Table 5). The results of BAI scores indicated a significant changes at p< 0/0001 (Table 6) and the t- test in the first, 10th session and the end of treatment (p< 0.0001, 0/0005, 0.001) (Table 7). The results of changes before and after treatment are given in Figure 1. As the figure demonstrates, there is a general decrease in all the scores after the treatments.

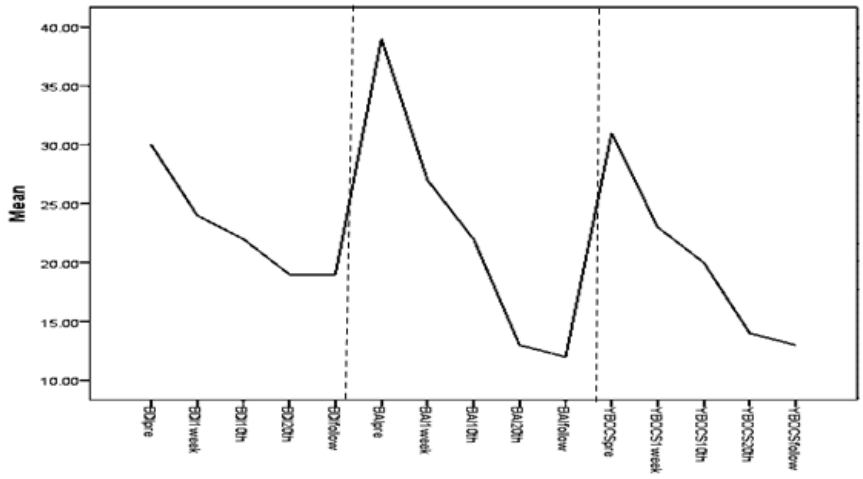

Figure 1. Changes in BDI, BAI and YBOCS scores before, after and in the one-month follow-up

Table 4. BDI results: changes in severity of symptoms based on Beck depression Scale

All patients	Pre	Post	One-month follow-up
Mean	30.0	19.0	19.0
Standard Deviation	6.0	1.0	1.0
F	29.0		
η2	0.68		
Significance	P<0.0001		

Table 5. Paired Samples Test in BDI scores

		Mean	Std. Deviation	t	sig
Pair 1	BDIpre	30.0	6.0	7.0	0.000
	BDI1week	24.0	6.0		
Pair 2	BDI1week	24.0	6.0	2.0	0.04
	BDI10th	22.0	4.0		
Pair 3	BDI10th	22.0	4.0	2.0	0.02
	BDI20th	19.0	1.0		
Pair 4	BDI20th	19.0	1.0	1.0	0.000
	BDIfollow	19.07	1.0		

Table 6. BAI results: changes in severity of symptoms based on Beck anxiety Scale

All patients	Pre	Post	One-month follow-up
Mean	39.0	13.0	12.0
Standard Deviation	5.0	4.0	4.0
F	108.0		
η2	0.85		
significance	P<0.0001		

Table 7. Paired Samples Test in BAI scores

		Mean	Std. Deviation	t	sig
Pair 1	BDIpre	39.0	5.0	7.0	0.000
	BDI1week	27.07	5.0		
Pair 2	BDI1week	27.07	5.0	3.0	0.005
	BDI10th	22.0	3.0		
Pair 3	BDI10th	22.0	3.0	5.0	0.000
	BDI20th	13.0	4.0		
Pair 4	BDI20th	13.0	4.0	1.0	0.000
	BDIfollow	12.0	4.0		

3.1. One-Month Follow-Up

One month after the subjects completed their treatment, they were followed up again. Of the 13 original patients, all have improved, 9 had mild symptoms with no severe dysfunction, and they did not feel the need to seek treatment in YBOCS score. In the BDI score, 2 patients were still depressed and had a decrease in their scores. The rest (10 patients) was without relapse. In the BAI score, 6 people were stable in their anxiety symptoms while the other patients were in the same condition or illustrated one or two different scores.

4. Discussion

In this case series study, we proposed a daycare program, including rTMS with Ex/PR and HRV biofeedback and examined its efficacy in 12 pharmaco-resistant OCD outpatients. The suggested treatment was included a standard CBT which emphasized ERP, rTMS on the supplementary area to control the compulsion (RP), and HRV biofeedback as a mindfulness module to maintain the beneficial effects of Ex and rTMS in relapse management after the treatments. Twelve patients were present at the daycare center at the same time (9 to 12 am) and received the treatments sequentially. Somewhere, there were their relatives and helped them with their exercises.

To our knowledge, this is the first study of multi-element treatments of OCD simultaneously. We observed a significant reduction in OCD symptoms and anxiety/depressive states after 20 sessions of the intensive program. Not only was there a significant improvement encouraged, but all of them showed normalization (even in one-month follow-up).

There were three novel findings of this study which can be considered as follows.

1- A rapid and significant reduction of symptoms was achieved after just one week of our proposed intensive program, much faster than what was previously seen by utilizing standard weekly CBT (Ex/RP) or pharmacotherapy or rTMS [25-27].

The efficacy of intensive and daily ERP for OCD is well established, and it is considered one of the standard and first-line treatments for OCD [28]. Intensive CBT and “therapy hours” produce improvement in up to 70 % of OCD patients for at least 4 weeks [29]. In a study conducted by Saxena *et al.* (2008), a significant change in normalized regional glucose metabolism was seen after brief intensive CBT compared to controls. OCD patients showed significant bilateral decreases in normalized thalamic metabolism with intensive CBT but had a significant increase in right dorsal anterior cingulate cortex activity that is strongly correlated with the degree of improvement in OCD symptoms after the 12th week. However, it has been thought that there is a need to produce the changes in symptoms or brain activity in as little as 4 weeks, and here is exactly the surprising point of our study that observed the first therapeutic response after the first week.

On the other hand, we applied brain stimulation to suppress the supplementary area to increase self-control. Although deep transcranial magnetic stimulation (dTMS) with the H7-coil was FDA-cleared for obsessive-compulsive disorder (OCD) in August 2018 based on multicenter sham-controlled studies [30], we applied this classical rTMS to targeting the cortex. The number of RCTs focusing on the SMA and OFC is increasing for OCD and rTMS [30]. The SMA may be a useful target for inhibitory stimulation in the treatment of OCD because it has extensive connections with regions implicated in cognitive processes and motor control [31]. Targeting the SMA with rTMs is correlated with the restoration of cortical inhibition which corresponds to intrusive thoughts, impulses, and repetitive motor responses [20, 32, 33]. Therefore, one explanation of the observed rapid response is that we targeted the multilateral circuit of OCD (CSTC). This means that TMS may have stimulated the cortical areas and Ex/RP and mindfulness based on biofeedback treatment could probably target other subcortical regions of this circuit.

2- Another interesting achievement of this study was the increasing patients' tolerance and reduction of distress by three factors simultaneously; rTMS, HRV biofeedback, and Ex/RP. As the results show, there was a significant reduction in anxiety scales of 12 patients. Lower Distress Tolerance (DT) is significantly associated with obsessions in nonclinical samples, poorer DT prospectively predicts the frequency of obsessions [34] and is associated with

greater anxiety following an experimental task designed to elicit an OCD-like intrusion [35]. Neuroimaging studies on OCD have identified hyperactivation during resting state and symptom provocation in a variety of cortical and subcortical regions, with recent meta-analyses emphasizing the role of the Orbitofrontal Cortex (OFC), Medial Frontal Cortex (MFC), anterior insula/frontal operculum (aI/fO), hippocampus, caudate nucleus, and thalamus [36, 37] when people have uncertainty and distress tolerance. With regard to the effect of rTMS on CSTC, this method can decrease DT through anxiety reduction [38, 39]. On the other hand, HRV is mediated by a complex interplay of the CNS and ANS subsystems, reflecting physiological functioning in a range of psychiatric disorders [40], with implications in emotion regulation and self-awareness [41]. HRV-biofeedback has been found to decrease stress and anxiety [42, 43], increase mindful awareness and self-compassion, and reduce rumination and worry [44-46]. Mindfulness psychotherapy which is called "third wave approaches" tends to reduce experiential avoidance, intolerance, and encouragement to remain in contact with the painful or distressing thoughts and emotions which arise during the course of treatment [47]. In fact, one of the reasons that patients do not tend to receive exposure is their intolerance of anxiety. People in this study received exposure and rTMS sequentially. They should exposure to their compulsion and quickly received to rTMS and tolerate its distress and focus on their breathing. Now the question is whether the stimulation of SMA has led to an increase in patient tolerance or not.

The hyperactivity of supplementary motor has been correlated with deficits in response inhibition in patients with OCD [48]. The rTMS stimulation parameters have been postulated to be the result of the inhibitory effects of low-frequency rTMS on hyperactive orbitofronto-striatal and/or supplementary motor circuits, the possible circuit that becomes dysfunctional to produce obsessions and compulsions of OCD [32]. Another explanation is due to the role of anxiety. OCD has heterogeneous features like ruminative and obsessive thoughts or compulsion and Intolerance Uncertainty (IU) [1].

The OCs engage themselves in compulsive rituals because of their IU and this construct plays a central role in anxiety and probably rTMS on SMA can reduce anxiety [49] and response inhibition subsequently.

3- In this study, we followed the patients up one month after exposure therapy. The results showed the significance of therapeutic effects among patients. Previous research has shown that exposure therapy has long-term effects on improving obsessive-compulsive disorder. Although exposure therapy is not a complete cure for OCD, adding other complementary elements can help to make it like a panacea for this disorder. According to the studies, the pathogenesis of OCD is different and involved a network of different areas of the brain. Hence, the best treatment would be to involve both the subcortical areas (bottom-up pathways) and the cortical areas (top-down pathways). rTMS adhere to exposure and maintain these effects with mindfulness-based biofeedback which has been found to have a significant impact on the treatment of OCD patients. Therefore, additional research is warranted to determine whether these adherences lead to greater symptom improvement.

There are some limitations to the findings. Because the proposed treatment has a multi-element nature, randomization in the design may potentially be considered a key strength of further studies. Therefore, these practical practices are not insuperable, and replication using an RCT is strongly suggested.

The generalization of our results has some limitations not only by the small sample size but also by the fact that these patients received an intensive treatment program which may suggest a high demand for changes.

Despite the limitations imposed by the characteristics of the short sample, inadequate follow-up period, the utilization of multi therapists for the procedures, the results suggest that our proposed daily intensive program has the potential to become an efficacious treatment for resistant OCD. Future studies are required to more rigorously evaluate the protocol through controlled trials with blinded assessment.

References

1- Michael H Bloch, Angeli Landeros-Weisenberger, Maria C Rosario, Christopher Pittenger, and James F Leckman, "Meta-analysis of the symptom structure of obsessive-compulsive disorder." *American Journal of Psychiatry*, Vol. 165 (No. 12), pp. 1532-42, (2008).

2- Rachel Middleton, Michael G Wheaton, Reilly Kayser, and H Blair Simpson, "Treatment resistance in obsessive-compulsive disorder." *Treatment resistance in psychiatry*, pp. 165-77, (2019).

3- Minah Kim, Wi Hoon Jung, Geumsook Shim, and Jun Soo Kwon, "The effects of selective serotonin reuptake inhibitors on brain functional networks during goal-directed planning in obsessive–compulsive disorder." *Scientific reports*, Vol. 10 (No. 1), pp. 1-8, (2020).

4- Gianluca Serafini *et al.*, "The effects of repetitive transcranial magnetic stimulation on cognitive performance in treatment-resistant depression. A systematic review." *Neuropsychobiology*, Vol. 71 (No. 3), pp. 125-39, (2015).

5- Marlene Taube-Schiff, Neil A Rector, Persephone Larkin, Adrienne Mehak, and Margaret A Richter, "Effectiveness of intensive treatment services for obsessive compulsive disorder: outcomes from the first Canadian residential treatment program." *International journal of psychiatry in clinical practice*, Vol. 24 (No. 1), pp. 59-67, (2020).

6- Iris Sijercic, Kristen M Whitfield, Stephanie E Cassin, and Martin M Antony, "A systematic review of cognitive-behavioral therapy for pharmacotherapy treatment-resistant obsessive-compulsive disorder." *Journal of Obsessive-Compulsive and Related Disorders*, Vol. 26p. 100532, (2020).

7- Lars-Göran Öst, Audun Havnen, Bjarne Hansen, and Gerd Kvale, "Cognitive behavioral treatments of obsessive–compulsive disorder. A systematic review and meta-analysis of studies published 1993–2014." *Clinical Psychology Review*, Vol. 40pp. 156-69, (2015).

8- Edna B Foa and Carmen P McLean, "The efficacy of exposure therapy for anxiety-related disorders and its underlying mechanisms: The case of OCD and PTSD." *Annual review of clinical psychology*, Vol. 12pp. 1-28, (2016).

9- Nathaniel Elkins-Brown, Rimma Teper, and Michael Inzlicht, "How mindfulness enhances self-control." in *Mindfulness in social psychology*: *Routledge*, (2017), pp. 65-78.

10- Fabrizio Didonna, "Mindfulness and obsessive-compulsive disorder: Developing a way to trust and validate one's internal experience." in *Clinical handbook of mindfulness*: *Springer*, (2009), pp. 189-219.

11- A Del Casale *et al.*, "Functional neuroimaging in obsessive-compulsive disorder." *Neuropsychobiology*, Vol. 64 (No. 2), pp. 61-85, (2011).

12- Mohammed R Milad and Scott L Rauch, "Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways." *Trends in cognitive sciences*, Vol. 16 (No. 1), pp. 43-51, (2012).

13- Tomohiro Nakao *et al.*, "Working memory dysfunction in obsessive–compulsive disorder: a neuropsychological and functional MRI study." *Journal of psychiatric research*, Vol. 43 (No. 8), pp. 784-91, (2009).

14- Andrea Bari and Trevor W Robbins, "Inhibition and impulsivity: behavioral and neural basis of response control." *Progress in neurobiology*, Vol. 108pp. 44-79, (2013).

15- Samuel R Chamberlain *et al.*, "Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives." *Science*, Vol. 321 (No. 5887), pp. 421-22, (2008).

16- Murat Yücel *et al.*, "Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder." *Archives of General Psychiatry*, Vol. 64 (No. 8), pp. 946-55, (2007).

17- Kun Li *et al.*, "Abnormal functional network of the thalamic subregions in adult patients with obsessive-compulsive disorder." *Behavioural brain research*, Vol. 371p. 111982, (2019).

18- Simone Rehn, Guy D Eslick, and Vlasios Brakoulias, "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)." *Psychiatric Quarterly*, Vol. 89 (No. 3), pp. 645-65, (2018).

19- Mandana Modirrousta *et al.*, "The efficacy of deep repetitive transcranial magnetic stimulation over the medial prefrontal cortex in obsessive compulsive disorder: Results from an open‐label study." *Depression and anxiety*, Vol. 32 (No. 6), pp. 445-50, (2015).

20- Antoine Pelissolo *et al.*, "Repetitive transcranial magnetic stimulation to supplementary motor area in refractory obsessive-compulsive disorder treatment: a sham-controlled trial." *International Journal of Neuropsychopharmacology*, Vol. 19 (No. 8), p. pyw025, (2016).

21- Young-Ji Lee, Bon-Hoon Koo, Wan-Seok Seo, Hye-Geum Kim, Ji-Yean Kim, and Eun-Jin Cheon, "Repetitive transcranial magnetic stimulation of the supplementary motor area in treatment-resistant obsessive-compulsive disorder: an open–label pilot study." *Journal of Clinical Neuroscience*, Vol. 44pp. 264-68, (2017).

22- Haisan Zhang *et al.*, "Altered functional connectivity between the cerebellum and the cortico-striato-thalamo-cortical circuit in obsessive-compulsive disorder." *Frontiers in psychiatry*, Vol. 10p. 522, (2019).

23- Steven I Rudoy, "Developing a model for understanding mindfulness as a potential intervention for obsessive-compulsive disorder." *Pepperdine University*, (2014).

24- Jonathan S Abramowitz, Edna B Foa, and Martin E Franklin, "Exposure and ritual prevention for obsessive-compulsive disorder: effects of intensive versus twice-

weekly sessions." *Journal of consulting and clinical psychology*, Vol. 71 (No. 2), p. 394, (2003).

25- Parth Dutta *et al.*, "Efficacy of intensive orbitofrontal continuous Theta Burst Stimulation (iOFcTBS) in Obsessive Compulsive Disorder: A Randomized Placebo Controlled Study." *Psychiatry Research*, Vol. 298p. 113784, (2021).

26- Madhuri H Nanjundaswamy, Shyam Sundar Arumugham, Janardhanan C Narayanaswamy, and YC Janardhan Reddy, "A prospective study of intensive in-patient treatment for obsessive-compulsive disorder." *Psychiatry Research*, Vol. 291, p. 113303, (2020).

27- Joseph O'Neill *et al.*, "Effects of intensive cognitive-behavioral therapy on cingulate neurochemistry in obsessive–compulsive disorder." *Journal of psychiatric research*, Vol. 47 (No. 4), pp. 494-504, (2013).

28- Hjalti Jónsson, Maria Kristensen, and Mikkel Arendt, "Intensive cognitive behavioural therapy for obsessive-compulsive disorder: a systematic review and meta-analysis." *Journal of Obsessive-Compulsive and related disorders*, Vol. 6, pp. 83-96, (2015).

29- Victoria B Oldfield, Paul M Salkovskis, and Tracey Taylor, "Time‐intensive cognitive behaviour therapy for obsessive‐compulsive disorder: A case series and matched comparison group." *British Journal of Clinical Psychology*, Vol. 50 (No. 1), pp. 7-18, (2011).

30- Harpreet Singh, Lorelei-Jane Wyman, Pegah Shojaii, and Leigh A Neal, "A Comparison of final Yale-Brown Obsessive-Compulsive Scale (YBOCS) in patients receiving either Repetitive Transcranial Magnetic Stimulation (rTMS) to the Right Dorsolateral Prefrontal Cortex+ Supplementary Motor Area (rDLPFC+ SMA) or Left Medial Orbitofrontal Cortex (FP1) for the treatment of Obsessive-Compulsive Disorder (OCD)." *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, Vol. 14 (No. 5), p. 1409, (2021).

31- Nathalie Picard and Peter L Strick, "Imaging the premotor areas." *Current opinion in neurobiology*, Vol. 11 (No. 6), pp. 663-72, (2001).

32- Emily R Hawken, Dancho Dilkov, Emil Kaludiev, Selcuk Simek, Felicia Zhang, and Roumen Milev, "Transcranial magnetic stimulation of the supplementary motor area in the treatment of obsessive-compulsive disorder: a multi-site study." *International journal of molecular sciences*, Vol. 17 (No. 3), p. 420, (2016).

33- C Nauczyciel *et al.*, "Repetitive transcranial magnetic stimulation over the orbitofrontal cortex for obsessive-compulsive disorder: a double-blind, crossover study." *Translational psychiatry*, Vol. 4 (No. 9), pp. e436-e36, (2014).

34- Jesse R Cougle, Kiara R Timpano, Kristin E Fitch, and Kirsten A Hawkins, "Distress tolerance and obsessions: an integrative analysis." *Depression and anxiety*, Vol. 28 (No. 10), pp. 906-14, (2011).

35- Jesse R Cougle, Kristin E Fitch, Frank D Fincham, Christina J Riccardi, Meghan E Keough, and Kiara R Timpano, "Excessive reassurance seeking and anxiety pathology: Tests of incremental associations and directionality." *Journal of anxiety disorders*, Vol. 26 (No. 1), pp. 117-25, (2012).

36- Jean-Yves Rotge *et al.*, "Provocation of obsessive–compulsive symptoms: a quantitative voxel-based meta-analysis of functional neuroimaging studies." *Journal of psychiatry & neuroscience: JPN*, Vol. 33 (No. 5), p. 405, (2008).

37- Stephen P Whiteside, John D Port, and Jonathan S Abramowitz, "A meta–analysis of functional neuroimaging in obsessive–compulsive disorder." *Psychiatry Research: Neuroimaging*, Vol. 132 (No. 1), pp. 69-79, (2004).

38- Flávia Paes *et al.*, "The value of repetitive transcranial magnetic stimulation (rTMS) for the treatment of anxiety disorders: an integrative review." *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, Vol. 10 (No. 5), pp. 610-20, (2011).

39- Reza Rostami *et al.*, "Efficacy and clinical predictors of response to rTMS treatment in pharmacoresistant obsessive-compulsive disorder (OCD): a retrospective study." *BMC psychiatry*, Vol. 20 (No. 1), pp. 1-13, (2020).

40- Tao Yang *et al.*, "Abnormal regional homogeneity of drug-naı̈ve obsessive-compulsive patients." *Neuroreport*, Vol. 21 (No. 11), pp. 786-90, (2010).

41- Stephen W Porges, "The polyvagal theory: phylogenetic substrates of a social nervous system." *International journal of psychophysiology*, Vol. 42 (No. 2), pp. 123-46, (2001).

42- Gregg Henriques, Steven Keffer, Craig Abrahamson, and S Jeanne Horst, "Exploring the effectiveness of a computer-based heart rate variability biofeedback program in reducing anxiety in college students." *Applied psychophysiology and biofeedback*, Vol. 36 (No. 2), pp. 101-12, (2011).

43- Paul Ratanasiripong, Kevin Sverduk, Judy Prince, and Diane Hayashino, "Biofeedback and counseling for stress and anxiety among college students." *Journal of College Student Development*, Vol. 53 (No. 5), pp. 742-49, (2012).

44- Alberto Chiesa and Alessandro Serretti, "Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis." *The journal of alternative and complementary medicine*, Vol. 15 (No. 5), pp. 593-600, (2009).

45- Willem Kuyken *et al.*, "How does mindfulness-based cognitive therapy work?" *Behaviour research and therapy*, Vol. 48 (No. 11), pp. 1105-12, (2010).

46- Clive J Robins, Shian‐Ling Keng, Andrew G Ekblad, and Jeffrey G Brantley, "Effects of mindfulness‐based stress reduction on emotional experience and expression: A randomized controlled trial." *Journal of clinical psychology*, Vol. 68 (No. 1), pp. 117-31, (2012).

47- Sapana R Patel, James Carmody, and H Blair Simpson, "Adapting mindfulness-based stress reduction for the treatment of obsessive-compulsive disorder: A case report." *Cognitive and Behavioral Practice*, Vol. 14 (No. 4), pp. 375-80, (2007).

48- Odile A Van Den Heuvel *et al.*, "Frontal-striatal dysfunction during planning in obsessive-compulsive disorder." *Archives of General Psychiatry*, Vol. 62 (No. 3), pp. 301-09, (2005).

49- Marcelo T Berlim, Nicholas H Neufeld, and Frederique Van den Eynde, "Repetitive transcranial magnetic stimulation (rTMS) for obsessive–compulsive disorder (OCD): An exploratory meta-analysis of randomized and sham-controlled trials." *Journal of psychiatric research*, Vol. 47 (No. 8), pp. 999-1006, (2013).