Title: Effectiveness of Low-Frequency rTMS and CBT in Reducing Symptoms Severity and Improving Cognitive Flexibility in Adults with OCD: A Clinical Trial

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Abstract

Background: This study aims to assess and compare the effects of low-frequency (LF) cognitive-behavioral therapy (CBT) and repetitive transcranial magnetic stimulation (rTMS) on symptoms and cognitive flexibility of adults with OCD.

Methods: This is a randomized clinical trial conducted on 24 people with OCD in Zanjan, Iran in two groups of CBT (n=12) and rTMS (n=12). The CBT with exposure and response prevention was presented at 20 sessions. The 1-Hz rTMS was delivered at 100 of resting MT using an 8-shaped coil over the right dorsolateral prefrontal cortex (F4) for 2 weeks at 10 sessions. They completed the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the Cognitive Flexibility Inventory before, immediately, and one month after the intervention. Collected data were analyzed in SPSS v.22 software.

Results: Results showed a significant difference between the two groups in the severity of OCD symptoms (obsessions and compulsions) immediately after intervention ($p<0.001$), where higher reductions were observed in the CBT group. There was no significant difference between the two groups in cognitive flexibility ($p>0.05$). No significant difference was found between the groups in any study variables one month after interventions.

Conclusion: There is a significant difference between CBT and LF rTMS techniques in reducing the severity of OCD symptoms, while there is no difference between them in improving cognitive flexibility of patients with OCD.

Keywords: Obsessive compulsive disorder, Cognitive behavioral therapy, Repetitive transcranial magnetic stimulation, Cognitive flexibility

Introduction

Obsessive-Compulsive Disorder (OCD) is a debilitating and severe mental disorder characterized by varying degrees of obsessive thoughts and behaviors. Obsessive thoughts are intrusive, unwanted, and annoying thoughts or images that people experience spontaneously that are not compatible with the person's obvious and perceived feelings. Compulsions are repetitive and time-consuming behaviors or mental acts that are used to neutralize anxiety caused by obsessive thoughts [1,2]. According to the World Health Organization, it is among the ten disabling disorders [3]. Its lifelong prevalence is 1-3% in the world [4] and 5.1-1.8% in Iran [5,6]. The OCD has a gradual onset and becomes chronic if people do not receive treatment [7], and its symptoms change over time due to stressors in life [8]. People with OCD tend to engage in obsessive actions, and even if they know that obsessive action are useless, they cannot stop it [9]. Impaired executive functioning has been observed frequently in OCD individuals [10]. Executive functioning is defined as the ability to manage intervening components in goal-directed behaviors and to predict the consequences of behavior [11]. Executive functions include cognitive processes such as working memory, inhibitory control, and cognitive flexibility that are essential for goal-directed behavior [12,13]. Clinically, people with OCD have difficulty switching between mental processes to generate adaptive behavioral responses to their symptoms. Many neurological studies have shown reduced cognitive flexibility in people with OCD [14,15]. The ability to modify cognitive sets to adapt to variable environmental stimuli is a key component in most operational definitions of cognitive flexibility. It is considered as a wide range of behaviors that enable people to behave adaptively in the face of stressful events instead of having maladaptive behaviors [16]. Recently, neurological models of OCD have suggested cognitive inflexibility as a major feature of OCD patients, which can also be present in their relatives [17]. Although OCD patients have many cognitive impairments, impaired cognitive flexibility may be an important trait for understanding the neural basis of OCD [18].

Cognitive-behavioral therapy (CBT) based on exposure and response prevention (ERP) is currently the standard treatment of OCD. In CBT, it is believed that individuals respond to the cognitive representation of stressful events, instead of responding to these events [19]. ERP involves gradual and long-term exposure to intimidating stimuli as well as the avoidance of obsessive actions [7]. CBT can reduce cortico-striato-thalamo-cortical (CSTC) circuit

hyperactivity and ultimately help improve the symptoms of OCD [20]. However, CBT is much less common than drug therapy. According to surveys in the United Kingdom and USA, only 5% of adults with OCD receive CBT [21]. On average, 30% of these patients refuse ERP therapy or drop out from treatment [22,23]. Therefore, complementary interventions have been suggested as an alternative to overcome CBT limitations in treatment of OCD. There is a potential new treatment option called repetitive transcranial magnetic stimulation (rTMS), that can modulate neural activity in brain circuits [24,25]. First introduced by Barker et al. in 1985, rTMS is a non-invasive technique that delivers electromagnetic pulses to selected areas of the cerebral cortex [26]. The rTMS can be applied at either high (≥5 Hz) or low (≤1 Hz) frequencies which have stimulatory and inhibitory effects on cortical excitability, respectively [27]. Studies have shown that dorsolateral prefrontal cortex (DLPFC) has an important role in cognitive flexibility [28,29]. Thus, improvement in DLPFC neuronal function may help improve cognitive flexibility of patients with OCD. In a clinical trial, Seo et al. reported the effectiveness of low-frequency (LF) rTMS over the right DLPFC in relieving the symptoms of OCD and depression in OCD patients [30].

Due to the high involvement of networks in the pathophysiology of OCD and the rTMS's ability to adjust cortical and subcortical structures and its potential therapeutic effectiveness in modulating inactive or hyperactive areas of the brain by targeting cortical circuits in patients with OCD, and lack of study on comparing the effectiveness of CBT and LF rTMS in treating OCD patients, the present study aims to compare the effects of CBT with ERP and rTMS over the right DLPFC on symptoms and cognitive flexibility in people with OCD. It is hypothesized that (a) there is difference between LF rTMS and CBT in reducing severity of OCD symptoms; (b) there is difference between LF rTMS and CBT in improving cognitive flexibility of OCD patients.

Methods

Study design and participants

This is a randomized clinical trial (Parallel, ID: IRCT20200805048316N1) with a pretest/posttest/follow-up design. The study population consists of all adults with OCD referred to the clinic of Shahid Beheshti Hospital in Zanjan, Iran in 2020 (during the COVID-19 pandemic) (n=41). The sample size was determined 13 for each group using GPower software by considering $\alpha = 0.05$, an error probability of 0.95 and an effect size of 0.6 according to previous studies in literature which reported middle-size to large-size effects of rTMS and CBT on patients with OCD

[31, 32]. Due to the COVID-19 pandemic and considering 20% dropout, the sample size was increased to 17 for each group. In this regard, 34 patients were selected using a convenience sampling method and randomly (by drawing cards) assigned into two parallel groups of CBT (n=17) and rTMS (n=17). Each group of patients were acknowledged which group s/he was assigned to. The randomization was conducted by a lottery method by the last author. All samples were diagnosed with OCD by a psychiatrist, and re-evaluated by a psychologist through a Structured Clinical Interview for DSM-5 (SCID-5) and using the Millon Clinical Multiaxial Inventory-III (MCMI-III). Inclusion criteria were: Having OCD according to the psychiatrist and based on SCID-5, at least a middle-school education, age 18-50 years, signing a written consent, and no history of psychological therapies, transcranial direct current stimulation or neurofeedback. On the other hand, exclusion criteria were: Existence of suicidal thoughts, personality disorders according to the SCID-5 and MCMI-III, psychotic disorders, history of seizures and epilepsy, existence of an electrical or metal object in the body (e.g. pacemaker), and having bipolar disorder. Before entering the study, the participants were receiving medication whose dosage had been stabilized for four weeks. After and during the study, the dosage was kept the same by the psychiatrist. Ten patients were excluded from the study (5 from the rTMS group and 5 from the CBT group). Therefore, 12 patients in each group completed the study. Figure 1 plots the sampling and allocation processes.

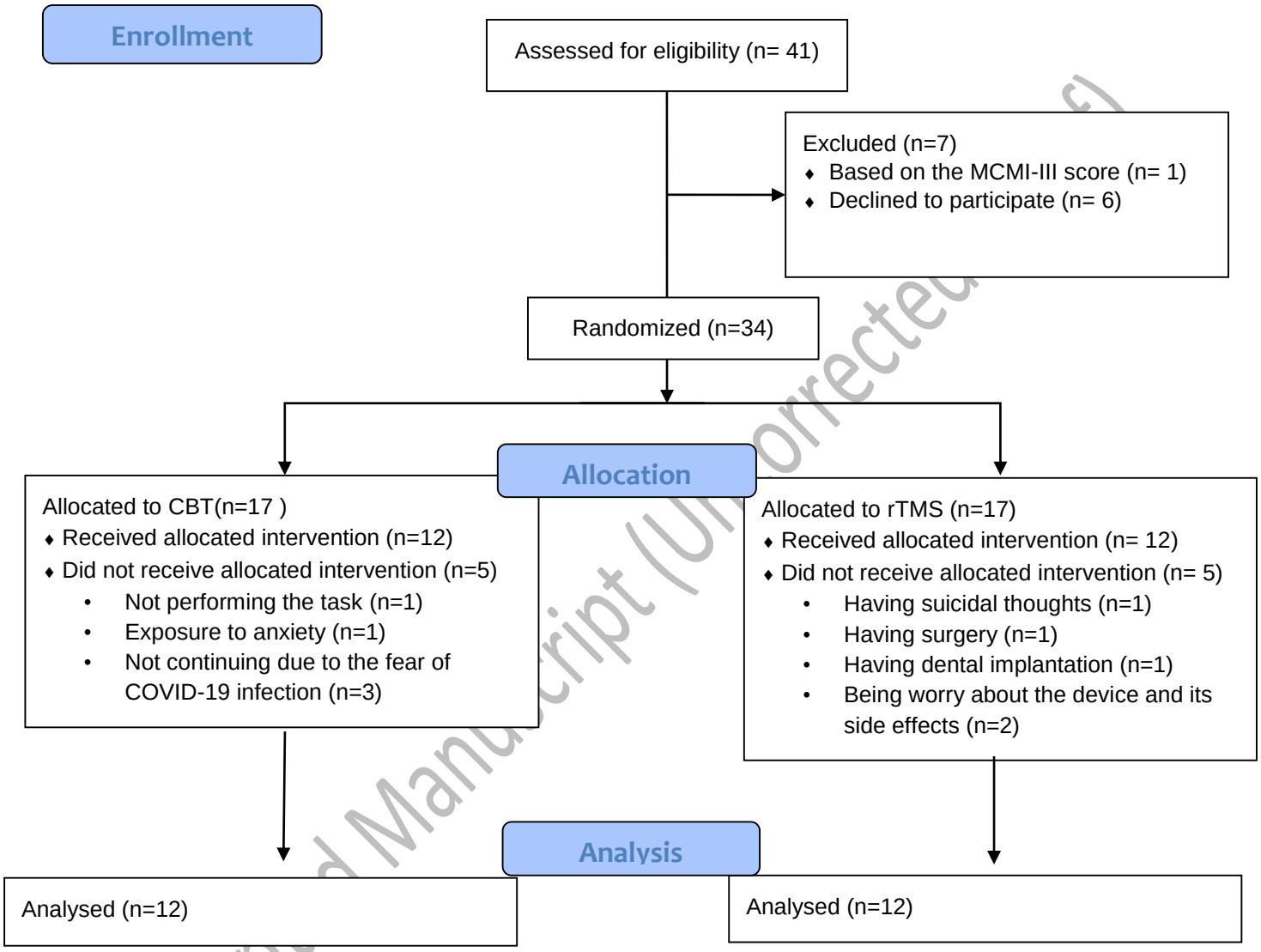

Figure 1.Flowchart of sampling and allocation

Measures

After obtaining a written informed consent from the participants, they completed a demographic form, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to assess their OCD symptoms and Cognitive Flexibility Inventory (CFI) to assess their cognitive flexibility. The Y-BOCS is a semi-structured interview and the gold standard for the measurement of OCD symptoms. It has two

primary scales, Symptom Checklist (SC) and Severity Scale (SS). The SC has 16 self-report items rated on a 5-point scale. In the SS, the severity of obsessions and compulsions are measured in five areas of distress, frequency, intervention, resistance, and symptom control. In this study, we used the Persian version of Y-BOCS validated by Rajezi Esfahani et al. [33] who reported internal consistency of 0.97 for the SC and 0.95 for the SS, a split-half reliability of 0.93 for the SC and 0.89 for the SS, and a test-retest reliability of 0.99. In our study, patients completed the SS scale only.

The CFI, developed by Dennis and Vander Wal [34], is a 20-item self-report tool using a 7-point Likert scale to measure three aspects of cognitive flexibility including the ability to perceive multiple alternative explanations for life occurrences and human behavior, the ability to generate multiple alternative solutions to difficult situations, and the desire to perceive difficult situations as controllable (Control subscale). The CFI has an excellent internal consistency and high test–retest reliability [34]. They reported a Cronbach's alpha of 0.90, 0.86, and 0.91, and a test-retest reliability of 0.81, 0.77, 0.75 for the overall scale, and control and alternatives subscales, respectively. For its Persian version, Shareh et al. [35] reported three-factor structure namely, control, alternative solutions and alternatives explanations. They reported the Cronbach's alpha and test-retest coefficients for the Persian CFI reliability as 0.90 and 0.71, respectively. The mentioned tools were completed again immediately and one month after the intervention.

Interventions

The CBT group individually received CBT with ERP at 20 sessions twice a week, each for 45-90 minutes according to the protocol proposed by Leahy et al [36] which is presented in Table 1. According to Jaurrieta et al. [37], individual CBT is more effective in reducing OCD symptoms than the group CBT. Treatment was performed by the researcher (MS student in clinical psychology) under the supervision of a therapist.

The rTMS group received rTMS for 2 weeks at 10 sessions (5 consecutive days per week, each for 20 minutes) according to protocol proposed by Gomes et al. [38]. Each person received 1-Hz rTMS at 100% of resting MT (1200 pulses/day with 10-min rest interval between each 300 pulses) using a focal 8-shaped 70-mm coil (Neuro-MS/D Advanced Therapeutic, Neurosoft Ltd., Russia) which was positioned on the right DLPFC (F4, according to the EEG 10–20 International System) such

that there was no space between the skin and the coil. The rTMS was conducted by an expert who was unaware of the results.

Data analysis

To analyze the collected data, descriptive statistics such as mean, standard deviation (SD), frequency, and percentage were used as well as inferential statistics such as chi-square test and independent t-test (to examine the differences in demographic factors and pretest means), MANCOVA (to compare the groups in terms of Y-BOCS and CFI scores), repeated-measures ANOVA (to compare the means of Y-BOCS and CFI between the time points), and Fisher's Least Significant Difference (LSD) test for pairwise comparison in SPSS v.22 software. According to the results of Kolmogorov-Smirnov test, the assumption of normal distribution of data in all three stages of pretest, posttest and follow-up was confirmed ($p > 0.05$). According to the results of Levene's test, the assumption of the quality of variances in the studied groups was not observed in in the posttest data of obsessions (component of Y-BOCS) and in the pre-test data of alternatives subscale of CFI ($p<0.05$). Therefore, in order to compare the two groups in the mentioned variables, the degree of corrected freedom was used. In other variables, the equality of variances was confirmed ($p > 0.05$).

Table 1. The protocol of CBT with ERP therapy

Sessions	Content
1-2	Acquaintance, a psychological interview, assessing current problems, symptoms, obsessions/compulsions, avoidance behaviors, feared consequences, internal and external triggers of obsessive thoughts, impairments in social, academic and occupational functioning; informing of diagnosis and treatment options, having patient write out goals for treatment (homework)
3-4	Review of homework and all obsessions/compulsions and avoided situations, assessing motivation for treatment, building motivation, describing cognitive-behavioral conceptualization of OCD and CBT, obtaining patient's commitment to proceed with treatment, introducing cognitive model, identifying automatic thoughts, obsessional anxiety, compulsions and triggering situations; evaluating automatic thoughts, asking patient to list advantages and disadvantages of proceeding with treatment (homework)
5-6	Review of homework, administering self-report questionnaires to assess mood and track progress, educating patient regarding intrusive thoughts as normal phenomena, evaluating the validity of automatic thoughts, helping patient devise behavioral experiments and begin constructing hierarchies of obsessions and avoided situations, having patient continue modifying automatic thoughts and assumptions, conduct behavioral experiments and practice in disrupting rituals (homework)
7-10	Review of homework, administering self-report questionnaires to assess mood and track progress, continue modifying automatic thoughts and dysfunctional assumptions, helping patient complete exposure hierarchies, planning initial exposure sessions, conducting exposure to initial items on hierarchies of obsessions and avoided situations, teaching postponing, slowing, and changing repetition, helping patient block all rituals, having patient continue modifying automatic thoughts, and assigning daily repetition of exposure (homework)
11-16	Review of homework, administering self-report questionnaires to assess mood and track progress, challenge any thoughts related to exposure avoidance and lapses in rituals, continue exposure to items higher up hierarchies of obsessions and avoided situations, continue to help patient block ritual, examining any lapses in response prevention, having patient continue modifying automatic thoughts, and assigning daily repetition of exposure (homework)
17-20	Review of homework, administering self-report questionnaires to assess mood and track progress, assessing attainment of goals to determine whether treatment may be tapered, tracking progress in identifying and modifying thoughts, assessing any life problems related to OCD or patient recovery, continue with cognitive challenges to schemas of danger, responsibility and the like; ensuring that the exposure is performed to items highest in the hierarchy, monitoring any lapses, teaching to use lapses to practice skills, encouraging patient to continue practicing all skills learned

Results

Characteristics of participants

Table 2 presents the demographic characteristics of patients. In the CBT group with a mean age of 32.83±9.43 years, there were two males and 10 females; 7 were single and 5 were married, and most of them had a bachelor's degree (n=7, 58.3%). In the rTMS group with a mean age of 30.17±11.26 years, there were 6 males and 6 females; 5 were single and 7 were married, and most of them had a high school diploma (n=5, 41.7%). No significant difference was found between the two groups in terms of gender (p= 0.083), marital status (p= 0.414) and level of education (p= 0.183) according to the results of chi-square test, and in terms of age (p=0.536) according to the results of independent t-test (Table 2). In the CBT group, 9 (75%) patients had contamination obsessions with washing/cleaning compulsion, 2 (16.16%) had harm obsessions with checking compulsions, and one (8.33%) had symmetry obsessions with ordering. In the rTMS group, 9 (75%) had contamination obsessions with washing/cleaning compulsion and 3 (25%) had harm obsessions with checking compulsions. However, this difference between groups was not significant according to the results of chi-square test (p>0.05).

Table 2. Demographic characteristics of the study participants

Characteristics		**CBT group (n=12)**	**rTMS group (n=12)**	**Total**	**Pearson Chi-Square**	**P-value***
		N(%)	**N(%)**	**N(%)**		
Gender	Male	2(16.7)	6(50)	8(33.3)	3	0.083
	Female	10(83.3)	6(50)	16(66.7)		
Marital status	Single	7(58.3)	5(41.7)	12(50)	0.67	0.414
	Married	5(41.7)	7(58.3)	12(50)		
Educational level	Lower than high school	1(8.3)	2(16.7)	3(12.5)	6.22	0.183
	Diploma	4(33.3)	5(41.7)	9(37.5)		
	Associate's degree	0(0)	1(8.3)	1(4.2)		
	Bachelor's degree	7(58.3)	2(16.7)	9(37.5)		
	Master's degree	0(0)	2(16.7)	2(8.3)		
Age (year)		**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**t**	**P-value****
		32.83±9.43	30.17±11.26	31.50±10.25	0.63	0.536

SD= Standard deviation, * Chi-square test, ** Independent t-test

Comparing OCD symptoms in two study groups

As can be seen from Figure 2, the pretest scores of Y-BOCS and its components were higher in the CBT group than in the rTMS group. This difference was statistically significant only in total score (p=0.011) and in the compulsions domain (p=0.017). Immediately after intervention, the scores highly decreased in both groups, where the decrease was higher in the CBT group. Results of MANCOVA (Table 3) showed that, after controlling the pretest scores, the difference between groups was statistically significant in posttest obsessions, $F(1,21)= 23.645$, $p<0.001$, $\eta^2=0.53$; posttest compulsions, $F(1,21)= 20.920$, $p<0.001$, $\eta^2=0.45$; and posttest total score, $F(1,21)= 25.565$, $p<0.001$, $\eta^2=0.55$. One month after intervention, these scores slightly increased in both groups. Results of repeated-measures ANOVA (Table 4) showed a significant difference in the Y-BOCS scores within three time points of pretest, posttest, and follow-up, where the main and interaction effects were significant (p<0.001). To assess between which time points this difference was observed, the LSD test was conducted. In the CBT group, the results (Table 5) showed a significant difference between pretest and posttest scores and between pretest and follow-up scores of obsessions, compulsions and total score (p<0.001) but there was no significant difference between posttest and follow-up scores (p>0.05). In the rTMS group, there was a significant difference between pretest and posttest scores and between pretest and follow-up scores of obsessions and total score (p<0.05) but not in compulsions. No significant differences between posttest and follow-up scores of any variables were observed in this group (Table 5).

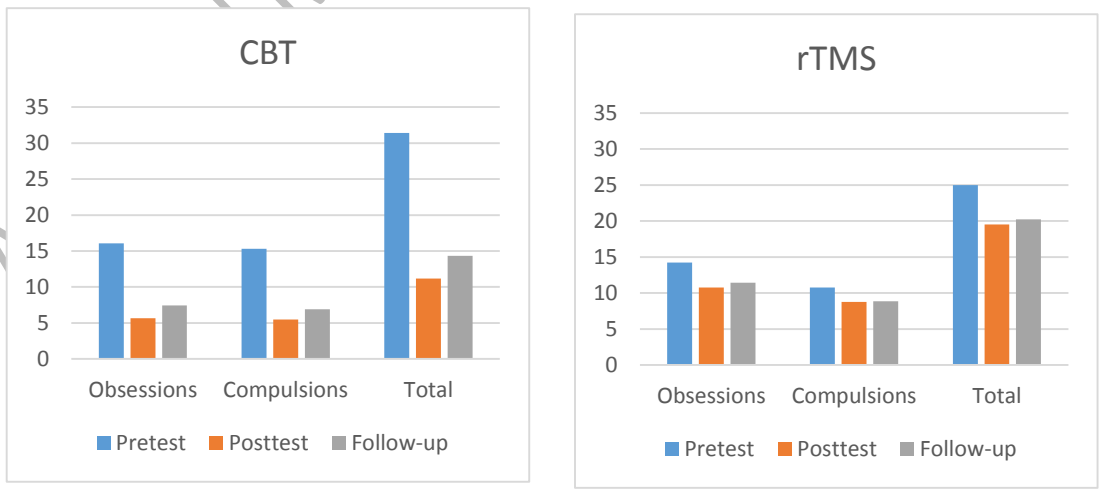

Figure 2. Mean scores of Y-BOCS for two study groups at three time points

Table 3. Test of between-subject effects (Dependent variable: Posttest OCD symptoms)

Source	Dependent variable	Sum of Squares	df	Mean Square	F	P value	Partial Eta squared
Pretest	Compulsions	225.054	1	225.054	22.700	.000	0.519
	Total	508.763	1	508.763	15.353	.001	0.422
Group	Obsessions	238.007	1	238.007	23.645	.000	0.530
	Compulsions	207.401	1	207.401	20.920	.000	0.499
	Total	847.182	1	847.182	25.565	.000	0.549
Error	Obsessions	211.383	21	10.066	-	-	-
	Compulsions	208.196	21	9.914	-	-	-
	Total	695.903	21	33.138	-	-	-

Table 4. Test of within-subject effects for OCD symptoms (Greenhouse-Geisser test)

Dependent variable		Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Obsessions	Time	663.528	1.834	361.834	65.249	.000	.748
	Time×Group	166.083	1.834	90.568	16.332	.000	.426
	Error	223.722	40.343	5.545	-	-	-
Compulsions	Time	498.111	1.991	250.145	48.251	.000	.687
	Time×Group	210.778	1.991	105.850	20.418	.000	.481
	Error	227.111	43.808	5.184	-	-	-
Total	Time	2310.194	1.949	1185.289	69.867	.000	.761
	Time×Group	751.028	1.949	385.329	22.713	.000	.508
	Error	727.444	42.879	16.965	-	-	-

Table 5. Pairwise comparison for OCD symptoms (LSD test)

	Group	(I) time	(J)time	Mean difference (I-J)	Std. Error	Sig.	95% CI	
							Lower bound	Upper bound
CBT	Obsessions	Pretest	Posttest	10.417*	1.003	.000	8.208	12.625
			Follow-up	8.667*	1.150	.000	6.135	11.199
		Posttest	Pretest	-10.417*	1.003	.000	-12.625	-8.208
			Follow-up	-1.750	.871	.070	-3.668	.168
		Follow-up	Pretest	-8.667*	1.150	.000	-11.199	-6.135
			Posttest	1.750	.871	.070	-.168	3.668
	Compulsions	Pretest	Posttest	9.833*	1.021	.000	7.586	12.081
			Follow-up	8.417*	.848	.000	6.550	10.283
		Posttest	Pretest	-9.833*	1.021	.000	-12.081	-7.586
			Follow-up	-1.417	.821	.112	-3.223	.390
		Follow-up	Pretest	-8.417*	.848	.000	-10.283	-6.550
			Posttest	1.417	.821	.112	-.390	3.223
	Total	Pretest	Posttest	20.250*	1.943	.000	15.974	24.526
			Follow-up	17.083*	1.885	.000	12.935	21.232
		Posttest	Pretest	-20.250*	1.943	.000	-24.526	-15.974
			Follow-up	-3.167	1.609	.075	-6.708	.374
		Follow-up	Pretest	-17.083*	1.885	.000	-21.232	-12.935
			Posttest	3.167	1.609	.075	-.374	6.708
rTMS	Obsessions	Pretest	Posttest	3.500*	.783	.001	1.776	5.224
			Follow-up	2.833*	.920	.010	.809	4.858
		Posttest	Pretest	-3.500*	.783	.001	-5.224	-1.776
			Follow-up	-.667	.732	.382	-2.277	.944
		Follow-up	Pretest	-2.833*	.920	.010	-4.858	-.809
			Posttest	.667	.732	.382	-.944	2.277
	Compulsions	Pretest	Posttest	2.000*	.826	.034	.183	3.817
			Follow-up	1.917	1.048	.095	-.389	4.223
		Posttest	Pretest	-2.000*	.826	.034	-3.817	-.183
			Follow-up	-.083	.973	.933	-2.224	2.058
		Follow-up	Pretest	-1.917	1.048	.095	-4.223	.389
			Posttest	.083	.973	.933	.183	3.817
	Total	Pretest	Posttest	5.500*	1.264	.001	2.717	8.283
			Follow-up	4.750*	1.670	.016	1.074	8.426
		Posttest	Pretest	-5.500*	1.264	.001	-8.283	-2.717
			Follow-up	-.750	1.493	.625	-4.036	2.536
		Follow-up	Pretest	-4.750*	1.670	.016	-8.426	-1.074
			Posttest	.750	1.493	.625	-2.536	4.036

*. The mean difference is significant at the .05 level.

Comparing cognitive flexibility in two study groups

As can be seen from Figure 3, the pretest scores of total CFI and its three subscales were higher in the CBT group than in the rTMS group, but there was no significant difference between the pretest CFI scores of the two groups ($p>0.05$). Immediately after the intervention, the total score and the scores of "alternative solutions" and "control" increased in both groups, while the score of "alternative explanations" subscale decreased in both groups. Results of MANCOVA (Table 6) showed that these difference between groups was not statistically significant in any domains ($p>0.05$). One month after intervention, a slight decrease was reported in the total score of CFI and its subscales in both groups. Results of repeated-measures ANOVA (Table 7) showed no significant overall difference between the two groups in any variables over three time points of pretest, posttest, and follow-up ($p>0.05$).

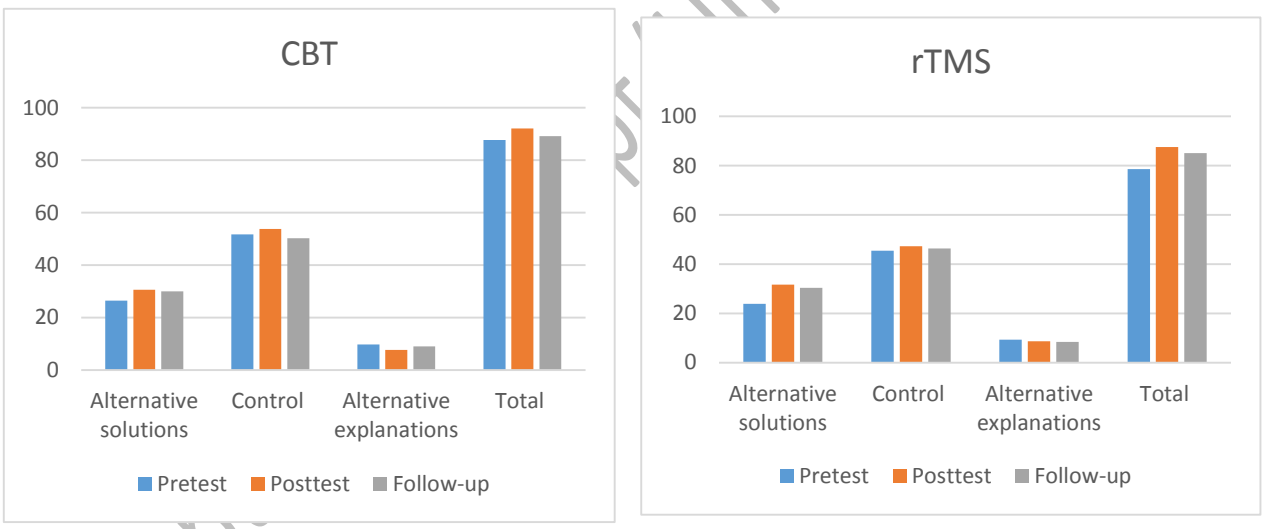

Figure 3. Mean scores of CFI for two study groups at three time points

Table 6. Test of between-subject effects (Dependent variable: cognitive flexibility)

Source	Dependent variable	Sum of Squares	df	Mean Square	F	Sig.	Partial Eta squared
Group	Alternative solutions	45.929	1	45.929	.614	.442	0.028
	Control	51.146	1	51.146	.517	.480	0.024
	Alternative explanations	6.782	1	6.782	1.811	.193	0.079
	Total	9.756	1	9.756	.048	.829	0.002
Error	Alternative solutions	1572.145	21	74.864			
	Control	2075.998	21	98.857			
	Alternative explanations	78.625	21	3.744			
	Total	4261.878	21	202.947			

Table 7. Test of within-subject effects for cognitive flexibility

Dependent variable		Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Alternative solutions	Time	498.694	1.576	316.330	3.281	.060	.130
	Time×Group	45.028	1.576	28.562	.296	.693	.013
	Error	3343.611	34.683	96.405			
Control	Time	71.861	1.577	45.557	.759	.447	.033
	Time×Group	24.694	1.577	15.655	.261	.719	.012
	Error	2082.778	34.702	60.019			
Alternative explanations	Time	20.361	2	10.181	2.057	.140	.086
	Time×Group	8.528	2	4.264	.861	.430	.038
	Error	217.778	44	4.949			
Total	Time	539.583	1.550	348.174	1.722	.198	.073
	Time×Group	95.583	1.550	61.677	.305	.683	.014
	Error	6895.500	34.095	202.247			

Discussion

The purpose of this study was to compare the effectiveness of CBT with ERP (presented individually) and LF (1-Hz) rTMS in reducing symptoms severity (Y-BOCS score) and improving cognitive inflexibility (CFI score) in 24 patients with OCD. The results showed that both treatment methods highly reduced the severity of OCD symptoms immediately after intervention, where CBT had higher effect. The difference between the results of two methods was statistically significant. This confirms our first hypothesis. After one month, the severity of symptoms was slightly increased in both groups, but it was not statistically significant. Grassi et al. [39] evaluated the potential CBT enhancing effect of high-frequency rTMS over the left DLPFC in patients with

OCD, and reported that the rTMS can be a tolerable tool to enhance the effect of CBT with ERP technique in these patients. In their study, at the end of the 16 CBT sessions (once a week), patients showed a 35% and 30% symptoms reduction in obsessions and compulsions, respectively. In our study, the means of obsessions and compulsions were reduced from 16.08 to 5.67 and from 15.33 to 5.50, respectively, after 20 CBT sessions. In a meta-analysis by Reid et al. [40], the effect of CBT with ERP on reducing OCD symptoms was reported high, which is consistent with our results. Elbeh et al. [24] in a clinical trial evaluated the effect of 1-Hz (LF) and 10-Hz (high frequency) rTMS on the right DLPFC in people with OCD. Their results showed that LF rTMS significantly reduced the Y-BOCS score, while this effect was not significant at a frequency of 10 Hz. Hence, they concluded that 1Hz-rTMS, targeting right DLPFC is a promising tool for treatment of OCD. Shayganfard et al. [41], Liang et al. [42], and Khedr et al. [43] also reported that LF rTMS over right DLPFC improved symptoms of OCD. These are consistent with our results. Seo et al. [30] examined the effect of rTMS on the right DLPFC (1 Hz, 1200 pulses per session, 100% of resting MT) for three weeks at 15 sessions in people with OCD. Their results also showed a significant decrease in Y-BOCS score. In Alonso et al.'s study [44], each OCD patient was given LF rTMS (1 Hz, 110% of resting MT) over the right DLPFC three times a week for 6 weeks. Their results did not show a significant decrease in the Y-BOCS score at the posttest and follow-up phases which is against our results. The discrepancy may be due to the shape of coil used for stimulation. They used a circular coil, while we used a figure-of-eight butterfly coil. The difference in the shape of coils can affect the inhibitory effect of 1-Hz rTMS [45]. According to Ørskov et al. [46], figure-of-eight coil may have better applicability in patients, due to the lower incidence of lack of inhibition in healthy subjects, and the lower experience of pain or discomfort. Another reasons for the discrepancy can be the difference in treatment sessions (10 sessions vs. 18 sessions) and stimulation intensity (100% vs. 110% of resting MT). In our study, the LF rTMS could significantly reduce obsessions in patients (from 14.25 to 10.75), but had no significant effect on their compulsions from pretest to follow-up phases; may be due to the stimulated area (right DLPFC), which is related to the cognitive circuit that influences obsessive thoughts, or not simulating the left DLPFC which has a role in inhibitory control of OCD patients [47]. Fremont et al. showed that volume loss in the left DLPFC is associated with the development of compulsive behaviours [48].

In comparing the effects of CBT and LF rTMS on the cognitive flexibility of adults with OCD, our results showed no significant difference between the two methods in improving the cognitive flexibility of patients. This rejects the second hypothesis of this study. Although the total score and the scores of "alternative solutions" and "control" components of the cognitive flexibility increased in both groups, but the difference was not statistically significant. In one study, Shayganfard et al. [41] found that executive functions (Wisconsin Card Sorting Test performance) were not improved after rTMS in 10 adults with OCD which is consistent with our results. No more related studies on OCD patients were found for the comparison of the results. The non-significant effect of LF rTMS on cognitive flexibility of OCD patients in our study may be because of the fact that the ability of rTMS is limited to penetrate and simulate the subcortical regions such as the thalamus and caudate nucleus, which have been suggested as anatomical neural substrates involved in OCD [47]. Regarding the non-significant effect of LF rTMS on cognitive flexibility of OCD patients, the reason may be because of the use of a self-report tool for the assessment of cognitive flexibility (i.e., the CFI). Compared to neuropsychological tests, self-report tools assess a different aspect of cognitive flexibility [49]. People with lower cognitive flexibility can still benefit from CBT, even though they are less able to use cognitive restructuring [50].

The present study had some limitations such as low sample size, no placebo or control group (since it was difficult to recruit patients during the COVID-19 pandemic), and not using objective assessment tool for assessing cognitive flexibility in patients. Most tests used in neuropsychological assessments to measure cognitive flexibility, such as Wisconsin test may not show well the more subtle cognitive problems that occur due to mental disorders [51]. Moreover, significant practical limitations reduce the clinical application of these tests. The Wisconsin test, for example, is time consuming in terms of execution and scoring and has a training effect and require an interactive relationship between the rater and the subject. As a result of training effect, patients' responses is not solely due to the effect of intervention. In this regard, we used a questionnaire (CFI) to measure cognitive flexibility of OCD patients. Moreover, the existence of comorbid diseases (i.e. depression) was not assessed. The parameters of LF rTMS (10 sessions, 1 Hz, 100% of MT, and 1200 pulses/day) may be suboptimal. They may also be not enough for generating antidepressant effects in patients. Furthermore, the generalization of the results to all OCD patients in Iran should be done with caution since this study was conducted on patients attending a clinic in a city of Iran (Zanjan). Further studies by simultaneous stimulation of

emotional and cognitive circuits in the brain and the use of larger sample size, a control/placebo group, and objective measurement tools such as functional magnetic resonance imaging and electroencephalography are recommended. We applied LF rTMS over the right DLPFC of patients. Future studies can use high-frequency rTMS or apply it over the left DLPFC to assess its efficacy compared to CBT with ERP.

Conclusion

There is significant difference between CBT and LF rTMS techniques in reducing the severity of OCD symptoms, but there is no difference between them in improving cognitive flexibility of patients with OCD.

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. Written informed consent was obtained from all patients for being included in the study. An ethical approval was obtained from the Research Ethics Committee of Zanjan University of Medical Sciences (Code: IR.ZUMS.REC.1399.180). This study was registered by Iranian Registry of Clinical Trials (parallel, ID: IRCT20200805048316N1, Registration date: 11/05/2020; https://en.irct.ir/trial/50734).

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors of this paper report no conflicts of interest in connection with this manuscript.

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Authors' contributions

AF: Assessing diagnostic criteria, conducting CBT, and writing; AZ: referring patients, supervision on rTMS, assessing inclusion/exclusion criteria, controlling the dosage and type of medications; RP: Referring patients, assessing inclusion/exclusion criteria, controlling the dosage

and type of medications; SR: Contribution in preparing initial draft; MD: Design, randomization, supervision. All authors approved the final draft

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